(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 March 2002 (21.03.2002)

PCT

(10) International Publication Number
WO 02/22577 A2

(51) International Patent Classification[7]: C07D 209/16, C07C 259/06, C07D 417/12, 403/12, 471/04, 519/00, 295/02, A61K 31/4045, 31/16, A61P 35/00

(21) International Application Number: PCT/EP01/10037

(22) International Filing Date: 30 August 2001 (30.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/229,943 1 September 2000 (01.09.2000) US
60/292,232 18 May 2001 (18.05.2001) US

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BAIR, Kenneth, Walter** [US/US]; 95 Melrose Road, Mountain Lakes, NJ 07046 (US). **GREEN, Michael, A.** [US/US]; 2180 Biddle Lane, Easton, PA 18040 (US). **PEREZ, Lawrence, B.** [US/US]; 12 Windsor Place, Hackettstown, NJ 07840 (US). **REMISZEWSKI, Stacy, W.** [US/US]; 147 Honeysuckle Drive, Washington Township, NJ 07676 (US). **SAMBUCETTI, Lidia** [US/US]; 32 Lone Mountain Court, Pacifica, CA 94044 (US). **VERSACE, Richard, William** [US/US]; 69 Townsend Road, Wanaque, NJ 07465 (US). **SHARMA, Sushil, Kumar** [US/US]; 9 Bakley Terrace, West Orange, NJ 07052 (US).

(74) Agent: **BECKER, Konrad**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/22577 A2

(54) Title: DEACETYLASE INHIBITORS

(57) **Abstract:** The present invention provides hydroxamate compounds which are deacetylase inhibitors. The compounds are suitable for pharmaceutical compositions having anti-proliferative properties.

DEACETYLASE INHIBITORS

The present invention relates to hydroxamate compounds which are inhibitors of histone deacetylase. The inventive compounds are useful as pharmaceuticals for the treatment of proliferative diseases.

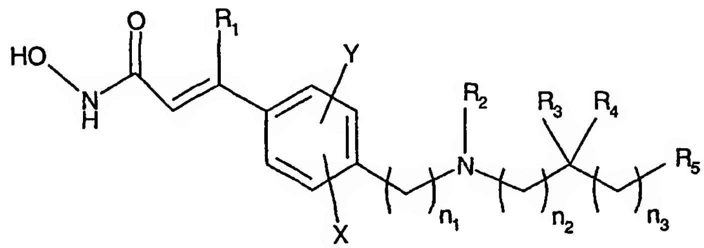
Background

Reversible acetylation of histones is a major regulator of gene expression that acts by altering accessibility of transcription factors to DNA. In normal cells, histone deacetylase (HDA) and histone acetyltrasferase together control the level of acetylation of histones to maintain a balance. Inhibition of HDA results in the accumulation of hyperacetylated histones, which results in a variety of cellular responses.

Inhibitors of HDA have been studied for their therapeutic effects on cancer cells. For example, butyric acid and its derivatives, including sodium phenylbutyrate, have been reported to induce apoptosis *in vitro* in human colon carcinoma, leukemia and retinoblastoma cell lines. However, butyric acid and its derivatives are not useful pharmacological agents because they tend to be metabolized rapidly and have a very short half-life *in vivo*. Other inhibitors of HDA that have been widely studied for their anti-cancer activities are trichostatin A and trapoxin. Trichostatin A is an antifungal and antibiotic and is a reversible inhibitor of mammalian HDA. Trapoxin is a cyclic tetrapeptide, which is an irreversible inhibitor of mammalian HDA. Although trichostatin and trapoxin have been studied for their anti-cancer activities, the *in vivo* instability of the compounds makes them less suitable as anti-cancer drugs. There remains a need for an active compound that is suitable for treating tumors, including cancerous tumors, that is highly efficacious and stable.

Summary

The present invention provides efficacious deacetylase inhibitor compounds that are useful as pharmaceutical agents having the formula I



(I)

wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl (especially methyl, ethyl or *n*-propyl, which methyl, ethyl and n-propyl substituents are unsubstituted or substituted by one or more substituents described below for alkyl substituents);

R_2 is selected from H, C_1-C_{10} alkyl, (e.g. methyl, ethyl or $-CH_2CH_2-OH$), C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, cycloalkylalkyl (e.g., cyclopropylmethyl), aryl, heteroaryl, arylalkyl (e.g. benzyl), heteroarylalkyl (e.g. pyridylmethyl), $-(CH_2)_nC(O)R_6$, $-(CH_2)_nOC(O)R_6$, amino acyl, HON-C(O)-CH=C(R_1)-aryl-alkyl- and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound represent C=O, C=S, or C=NR_8, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound can form a C_4-C_9 heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl (e.g. benzyl), heteroarylalkyl (e.g. pyridylmethyl), aromatic polycycles, non-aromatic polycycles, mixed aryl and non-aryl polycycles, polyheteroaryl, non-aromatic polyheterocycles, and mixed aryl and non-aryl polyheterocycles;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0 – 6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, such as CH_3 and CF_3, NO_2, C(O)R_1, OR_9, SR_9, CN, and $NR_{10}R_{11}$;

R_6 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl (e.g., cyclopropylmethyl), aryl, heteroaryl, arylalkyl (e.g., benzyl, 2-phenylethenyl), heteroarylalkyl (e.g., pyridylmethyl), OR_{12}, and $NR_{13}R_{14}$;

R_7 is selected from OR_{15}, SR_{15}, $S(O)R_{16}$, SO_2R_{17}, $NR_{13}R_{14}$, and $NR_{12}SO_2R_6$;

R_8 is selected from H, OR_{15}, $NR_{13}R_{14}$, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl (e.g., benzyl), and heteroarylalkyl (e.g., pyridylmethyl);

R_9 is selected from $C_1 - C_4$ alkyl, for example, CH_3 and CF_3, C(O)-alkyl, for example $C(O)CH_3$, and $C(O)CF_3$;

R_{10} and R_{11} are the same or different and independently selected from H, C_1-C_4 alkyl, and -C(O)-alkyl;

R_{12} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, $C_4 - C_9$ heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl (e.g., benzyl), and heteroarylalkyl (e.g., pyridylmethyl);

R_{13} and R_{14} are the same or different and independently selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl (e.g., benzyl), heteroarylalkyl (e.g., pyridylmethyl), amino acyl, or R_{13} and R_{14} together with the nitrogen to which they are bound are $C_4 - C_9$ heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R_{15} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{16} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{17} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, aromatic polycycles, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and $NR_{13}R_{14}$;

m is an integer selected from 0 to 6; and

Z is selected from O, NR_{13}, S and S(O),

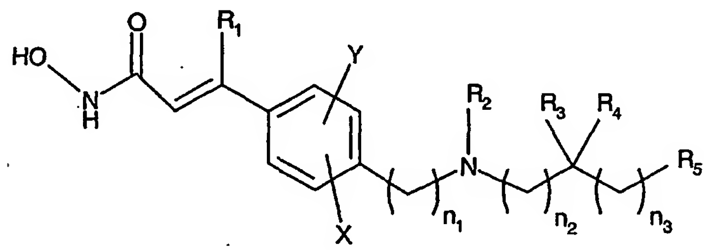
or a pharmaceutically acceptable salt thereof.

The compounds of the present invention are suitable as active agents in pharmaceutical compositions that are efficacious particularly for treating cellular proliferative ailments. The pharmaceutical composition has a pharmaceutically effective amount of the

present active agent along with other pharmaceutically acceptable exipients, carriers, fillers, diluents and the like. The term pharmaceutically effective amount as used herein indicates an amount necessary to administer to a host to achieve a therapeutic result, especially an anti-tumor effect, e.g., inhibition of proliferation of malignant cancer cells, benign tumor cells or other proliferative cells.

Detailed Description

The present invention provides hydroxamate compounds, e.g., hydroxamic acids, that are inhibitors of deacetylases, preferably inhibitors of histone deacetylases. The hydroxamate compounds are highly suitable for treating tumors, including cancerous tumors. The hydroxamate compounds of the present invention have the following structure I



(I)

wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl (especially methyl, ethyl or *n*-propyl, which methyl, ethyl and n-propyl substituents are unsubstituted or substituted by one or more substituents described below for alkyl substituents);

R_2 is selected from H, C_1-C_{10} alkyl, (preferably C_1-C_6 alkyl, e.g. methyl, ethyl or $-CH_2CH_2-OH$), C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, cycloalkylalkyl (e.g., cyclopropylmethyl), aryl, heteroaryl, arylalkyl (e.g. benzyl), heteroarylalkyl (e.g. pyridylmethyl), $-(CH_2)_nC(O)R_6$, $-(CH_2)_nOC(O)R_6$, amino acyl, HON-C(O)-CH=C(R_1)-aryl-alkyl- and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound represent C=O, C=S, or C=NR_8, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound can form a C_4-C_9 heterocycloalkyl, a

heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl (e.g. benzyl), heteroarylalkyl (e.g. pyridylmethyl), aromatic polycycles, non-aromatic polycycles, mixed aryl and non-aryl polycycles, polyheteroaryl, non-aromatic polyheterocycles, and mixed aryl and non-aryl polyheterocycles;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0 – 6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, such as CH_3 and CF_3, NO_2, $C(O)R_1$, OR_9, SR_9, CN, and $NR_{10}R_{11}$;

R_6 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl (e.g., cyclopropylmethyl), aryl, heteroaryl, arylalkyl (e.g., benzyl, 2-phenylethenyl), heteroarylalkyl (e.g., pyridylmethyl), OR_{12}, and $NR_{13}R_{14}$;

R_7 is selected from OR_{15}, SR_{15}, $S(O)R_{16}$, SO_2R_{17}, $NR_{13}R_{14}$, and $NR_{12}SO_2R_6$;

R_8 is selected from H, OR_{15}, $NR_{13}R_{14}$, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl (e.g., benzyl), and heteroarylalkyl (e.g., pyridylmethyl);

R_9 is selected from $C_1 - C_4$ alkyl, for example, CH_3 and CF_3, C(O)-alkyl, for example $C(O)CH_3$, and $C(O)CF_3$;

R_{10} and R_{11} are the same or different and independently selected from H, C_1-C_4 alkyl, and -C(O)-alkyl;

R_{12} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, $C_4 - C_9$ heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl (e.g., benzyl), and heteroarylalkyl (e.g., pyridylmethyl);

R_{13} and R_{14} are the same or different and independently selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl (e.g., benzyl), heteroarylalkyl (e.g., pyridylmethyl), amino acyl, or R_{13} and R_{14} together with the nitrogen to which they are bound are $C_4 - C_9$ heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R_{15} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{16} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{17} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, aromatic polycycles, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and $NR_{13}R_{14}$;

m is an integer selected from 0 to 6; and

Z is selected from O, NR_{13}, S and S(O),

or a pharmaceutically acceptable salt thereof.

As appropriate, unsubstituted means that there is no substituent or that the only substituents are hydrogen.

Halo substituents are selected from fluoro, chloro, bromo and iodo, preferably fluoro or chloro.

Alkyl substituents include straight and branched C_1-C_6alkyl, unless otherwise noted. Examples of suitable straight and branched C_1-C_6alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, and the like. Unless otherwise noted, the alkyl substituents include both unsubstituted alkyl groups and alkyl groups that are substituted by one or more suitable substituents, including unsaturation (i.e. there are one or more double or triple C-C bonds), acyl, cycloalkyl, halo, oxyalkyl, alkylamino, aminoalkyl, acylamino and OR_{15}, for example, alkoxy. Preferred substituents for alkyl groups include halo, hydroxy, alkoxy, oxyalkyl, alkylamino, and aminoalkyl.

Cycloalkyl substituents include C_3-C_9 cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. Unless otherwise noted, cycloalkyl substituents include both unsubstituted cycloalkyl groups and cycloalkyl groups that are substituted by one or more suitable substituents, including C_1-C_6 alkyl, halo, hydroxy, aminoalkyl, oxyalkyl, alkylamino, and OR_{15}, such as alkoxy. Preferred substituents for cycloalkyl groups include halo, hydroxy, alkoxy, oxyalkyl, alkylamino and aminoalkyl.

The above discussion of alkyl and cycloalkyl substituents also applies to the alkyl portions of other substituents, such as without limitation, alkoxy, alkyl amines, alkyl ketones, arylalkyl, heteroarylalkyl, alkylsulfonyl and alkyl ester substituents and the like.

Heterocycloalkyl substituents include 3 to 9 membered aliphatic rings, such as 4 to 7 membered aliphatic rings, containing from one to three heteroatoms selected from nitrogen, sulfur and oxygen. Examples of suitable heterocycloalkyl substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, and 1,4-oxathiapane. Unless otherwise noted, the rings are unsubstituted or substuted on the carbon atoms by one or more suitable substituents, including C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, aryl, heteroaryl, arylalkyl (e.g., benzyl), and heteroarylalkyl (e.g., pyridylmethyl), halo, amino, alkyl amino and OR_{15}, for example alkoxy. Unless otherwise noted, nitrogen heteroatoms are unsubstituted or substituted by H, C_1-C_4 alkyl, arylalkyl (e.g., benzyl), and heteroarylalkyl (e.g., pyridylmethyl), acyl, aminoacyl, alkylsulfonyl, and arylsulfonyl.

Cycloalkylalkyl substituents include compounds of the formula $-(CH_2)_{n5}$-cycloalkyl wherein n5 is a number from 1-6. Suitable cycloalkylalkyl substituents include cyclopentylmethyl-, cyclopentylethyl, cyclohexylmethyl and the like. Such substituents are unsubstituted or substituted in the alkyl portion or in the cycloalkyl portion by a suitable substituent, including those listed above for alkyl and cycloalkyl.

Aryl substituents include unsubstituted phenyl and phenyl substituted by one or more suitable substituents, including C_1-C_6 alkyl, cycloalkylalkyl (e.g., cyclopropylmethyl), O(CO)alkyl, oxyalkyl, halo, nitro, amino, alkylamino, aminoalkyl, alkyl ketones, nitrile, carboxyalkyl, alkylsulfonyl, aminosulfonyl, arylsulfonyl, and OR_{15}, such as alkoxy. Preferred substituents include including C_1-C_6 alkyl, cycloalkyl (e.g., cyclopropylmethyl), alkoxy, oxyalkyl, halo, nitro, amino, alkylamino, aminoalkyl, alkyl ketones, nitrile, carboxyalkyl, alkylsulfonyl, arylsulfonyl, and aminosulfonyl. Examples of suitable aryl groups include C_1-C_4alkylphenyl, C_1-C_4alkoxyphenyl, trifluoromethylphenyl, methoxyphenyl, hydroxyethylphenyl, dimethylaminophenyl, aminopropylphenyl, carbethoxyphenyl, methanesulfonylphenyl and tolylsulfonylphenyl.

Aromatic polycycles include naphthyl, and naphthyl substituted by one or more suitable substituents, including C_1-C_6 alkyl, cycloalkylalkyl (e.g., cyclopropylmethyl), oxyalkyl, halo, nitro, amino, alkylamino, aminoalkyl, alkyl ketones, nitrile, carboxyalkyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl and OR_{15}, such as alkoxy.

Heteroaryl substituents include compounds with a 5 to 7 member aromatic ring containing one or more heteroatoms, for example from 1 to 4 heteroatoms, selected from N, O and S. Typical heteroaryl substituents include furyl, thienyl, pyrrole, pyrazole, triazole, thiazole, oxazole, pyridine, pyrimidine, isoxazolyl, pyrazine and the like. Unless otherwise noted, heteroaryl substituents are unsubstituted or substituted on a carbon atom by one or more suitable substituents, including alkyl, the alkyl substituents identified above, and another heteroaryl substituent. Nitrogen atoms are unsubstituted or substituted, for example by R_{13}; especially useful N substituents include H, $C_1 - C_4$ alkyl, acyl, aminoacyl, and sulfonyl.

Arylalkyl substituents include groups of the formula $-(CH_2)_{n5}$-aryl, $-(CH_2)_{n5-1}$-(CHaryl)-$(CH_2)_{n5}$-aryl or $-(CH_2)_{n5-1}CH$(aryl)(aryl) wherein aryl and n5 are as defined above. Such arylalkyl substituents include benzyl, 2-phenylethyl, 1-phenylethyl, tolyl-3-propyl, 2-phenylpropyl, diphenylmethyl, 2-diphenylethyl, 5,5-dimethyl-3-phenylpentyl and the like. Arylalkyl substituents are unsubstituted or substituted in the alkyl moiety or the aryl moiety or both as described above for alkyl and aryl substituents.

Heteroarylalkyl substituents include groups of the formula $-(CH_2)_{n5}$-heteroaryl wherein heteroaryl and n5 are as defined above and the bridging group is linked to a carbon or a nitrogen of the heteroaryl portion, such as 2-, 3- or 4-pyridylmethyl, imidazolylmethyl, quinolylethyl, and pyrrolylbutyl. Heteroaryl substituents are unsubstituted or substituted as discussed above for heteroaryl and alkyl substituents.

Amino acyl substituents include groups of the formula $-C(O)-(CH_2)_n-C(H)(NR_{13}R_{14})-(CH_2)_n-R_5$ wherein n, R_{13}, R_{14} and R_5 are described above. Suitable aminoacyl substituents include natural and non-natural amino acids such as glycinyl, D-tryptophanyl, L-lysinyl, D- or L-homoserinyl, 4-aminobutryic acyl, $\pm$-3-amin-4-hexenoyl.

Non-aromatic polycycle substituents include bicyclic and tricyclic fused ring systems where each ring can be 4-9 membered and each ring can contain zero, 1 or more double and/or triple bonds. Suitable examples of non-aromatic polycycles include decalin, octahydroindene, perhydrobenzocycloheptene, perhydrobenzo-[*f*]-azulene. Such substituents are unsubstituted or substituted as described above for cycloalkyl groups.

Mixed aryl and non-aryl polycycle substituents include bicyclic and tricyclic fused ring systems where each ring can be 4 – 9 membered and at least one ring is aromatic. Suitable examples of mixed aryl and non-aryl polycycles include methylenedioxyphenyl, *bis*-methylenedioxyphenyl, 1,2,3,4-tetrahydronaphthalene, dibenzosuberane, dihdydroanthracene, 9H-fluorene. Such substituents are unsubstituted or substituted by nitro or as described above for cycloalkyl groups.

Polyheteroaryl substituents include bicyclic and tricyclic fused ring systems where each ring can independently be 5 or 6 membered and contain one or more heteroatom, for example, 1, 2, 3, or 4 heteroatoms, chosen from O, N or S such that the fused ring system is aromatic. Suitable examples of polyheteroaryl ring systems include quinoline, isoquinoline, pyridopyrazine, pyrrolopyridine, furopyridine, indole, benzofuran, benzothiofuran, benzindole, benzoxazole, pyrroloquinoline, and the like. Unless otherwise noted, polyheteroaryl substituents are unsubstituted or substituted on a carbon atom by one or more suitable substituents, including alkyl, the alkyl substituents identified above and a substituent of the formula $-O-(CH_2CH=CH(CH_3)(CH_2))_{1-3}H$. Nitrogen atoms are unsubstituted or substituted, for example by R_{13}; especially useful N substituents include H, $C_1 - C_4$ alkyl, acyl, aminoacyl, and sulfonyl.

Non-aromatic polyheterocyclic substituents include bicyclic and tricyclic fused ring systems where each ring can be 4 – 9 membered, contain one or more heteroatom, for example, 1, 2, 3, or 4 heteroatoms, chosen from O, N or S and contain zero or one or more C-C double or triple bonds. Suitable examples of non-aromatic polyheterocycles include hexitol, cis-perhydro-cyclohepta[b]pyridinyl, decahydro-benzo[f][1,4]oxazepinyl, 2,8-dioxabicyclo[3.3.0]octane, hexahydro-thieno[3,2-b]thiophene, perhydropyrrolo[3,2-b]pyrrole, perhydronaphthyridine, perhydro-1H-dicyclopenta[b,e]pyran. Unless otherwise noted, non-aromatic polyheterocyclic substituents are unsubstituted or substituted on a carbon atom by one or more substituents, including alkyl and the alkyl substituents identified above.

Nitrogen atoms are unsubstituted or substituted, for example, by R_{13}; especially useful N substituents include H, $C_1 - C_4$ alkyl, acyl, aminoacyl, and sulfonyl.

Mixed aryl and non-aryl polyheterocycles substituents include bicyclic and tricyclic fused ring systems where each ring can be 4 – 9 membered, contain one or more heteroatom chosen from O, N or S, and at least one of the rings must be aromatic. Suitable examples of mixed aryl and non-aryl polyheterocycles include 2,3-dihydroindole, 1,2,3,4-tetrahydroquinoline, 5,11-dihydro-10H-dibenz[b,e][1,4]diazepine, 5H-dibenzo[b,e][1,4]diazepine, 1,2-dihydropyrrolo[3,4-b][1,5]benzodiazepine, 1,5-dihydro-pyrido[2,3-b][1,4]diazepin-4-one, 1,2,3,4,6,11-hexahydro-benzo[b]pyrido[2,3-e][1,4]diazepin-5-one. Unless otherwise noted, mixed aryl and non-aryl polyheterocyclic substituents are unsubstituted or substituted on a carbon atom by one or more suitable substituents, including, -N-OH, =N-OH, alkyl and the alkyl substituents identified above. Nitrogen atoms are unsubstituted or substituted, for example, by R_{13}; especially useful N substituents include H, $C_1 - C_4$ alkyl, acyl, aminoacyl, and sulfonyl.

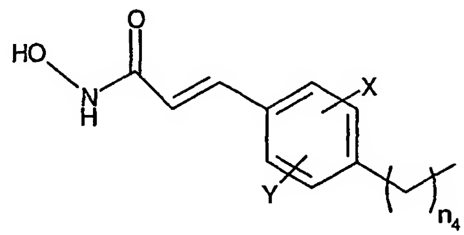
Amino substituents include primary, secondary and tertiary amines and in salt form, quaternary amines. Examples of amino substituents include mono- and di-alkylamino, mono- and di-aryl amino, mono- and di-arylalkyl amino, aryl-arylalkylamino, alkyl-arylamino, alkyl-arylalkylamino and the like.

Sulfonyl substituents include alkylsulfonyl and arylsulfonyl, for example methane sulfonyl, benzene sulfonyl, tosyl and the like.

Acyl substituents include groups of the formula –C(O)-W, –OC(O)-W, –C(O)-O-W and –C(O)N$R_{13}R_{14}$, where W is R_{16}, H or cycloalkylalkyl.

Acylamino substituents include groups of the formula –N(R_{12})C(O)-W, –N(R_{12})C(O)-O-W, and –N(R_{12})C(O)-NHOH and R_{12} and W are as defined above.

The R_2 substituent HON-C(O)-CH=C(R_1)-aryl-alkyl- is a group of the formula



wherein n_4 is 0-3 and X and Y are as defined above.

Preferences for each of the substituents include the following:

R_1 is H, halo, or a straight chain C_1-C_4 alkyl;

R_2 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, amino acyl, and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently selected from H, and C_1-C_6 alkyl, or R_3 and R_4 together with the carbon to which they are bound represent C=O, C=S, or $C=NR_8$;

R_5 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, an aromatic polycycle, a non-aromatic polycycle, a mixed aryl and non-aryl polycycle, polyheteroaryl, a non-aromatic polyheterocycle, and a mixed aryl and non-aryl polyheterocycle;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0 – 6, when n_1 is 1-6, each carbon atom is unsubstituted or independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, CF_3, NO_2, $C(O)R_1$, OR_9, SR_9, CN, and $NR_{10}R_{11}$;

R_6 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR_{12}, and $NR_{13}R_{14}$;

R_7 is selected from OR_{15}, SR_{15}, $S(O)R_{16}$, SO_2R_{17}, $NR_{13}R_{14}$, and $NR_{12}SO_2R_6$;

R_8 is selected from H, OR_{15}, $NR_{13}R_{14}$, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R_9 is selected from $C_1 - C_4$ alkyl and C(O)-alkyl;

R_{10} and R_{11} are the same or different and independently selected from H, C_1-C_4 alkyl, and -C(O)-alkyl;

R_{12} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R_{13} and R_{14} are the same or different and independently selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and amino acyl;

R_{15} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{16} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

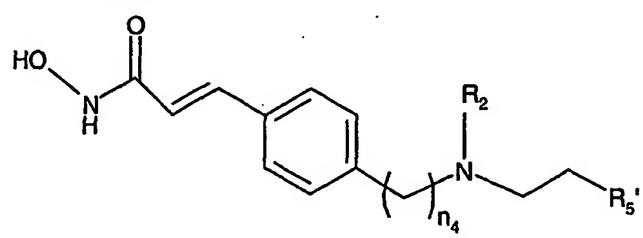
R_{17} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $NR_{13}R_{14}$;

m is an integer selected from 0 to 6; and

Z is selected from O, NR_{13}, S, S(O).

Useful compounds of the formula I include those wherein each of R_1, X, Y, R_3, and R_4 is H, including those wherein one of n_2 and n_3 is zero and the other is 1, especially those wherein R_2 is H or $-CH_2-CH_2-OH$.

One suitable genus of hydroxamate compounds are those of formula Ia



(Ia)

wherein

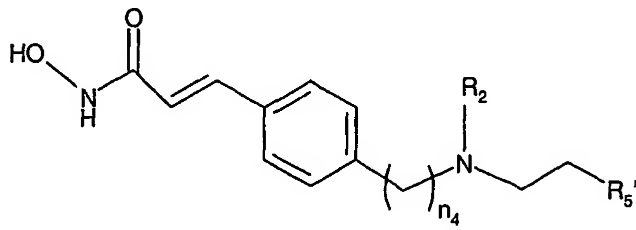
n_4 is 0-3,

R_2 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, amino acyl and $-(CH_2)_nR_7$;

R_5' is heteroaryl, heteroarylalkyl (e.g., pyridylmethyl), aromatic polycycles, non-aromatic polycycles, mixed aryl and non-aryl polycycles, polyheteroaryl, or mixed aryl and non-aryl polyheterocycles,

or a pharmaceutically acceptable salt thereof.

Another suitable genus of hydroxamate compounds are those of formula Ia



(Ia)

wherein

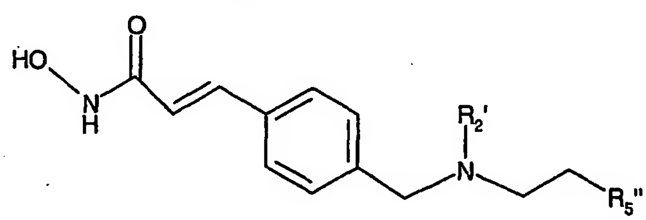
n_4 is 0-3,

R_2 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, -$(CH_2)_nC(O)R_6$, amino acyl and -$(CH_2)_nR_7$;

R_5' is aryl, arylalkyl, aromatic polycycles, non-aromatic polycycles, and mixed aryl and non-aryl polycycles; especially aryl, such as p-fluorophenyl, p-chlorophenyl, p-O-C_1-C_4-alkylphenyl, such as p-methoxyphenyl, and p-C_1-C_4-alkylphenyl; and arylalkyl, such as benzyl, *ortho, meta or para*-fluorobenzyl, *ortho, meta or para*-chlorobenzyl, *ortho, meta or para*-mono, di or tri-O-C_1-C_4-alkylbenzyl, such as *ortho, meta or para*-methoxybenzyl, *m,p*-diethoxybenzyl, *o,m,p*-triimethoxybenzyl , and *ortho, meta or para*- mono, di or tri C_1-C_4-alkylphenyl, such as *p*-methyl, *m,m*-diethylphenyl,

or a pharmaceutically acceptable salt thereof.

Another interesting genus are the compounds of formula Ib



(Ib)

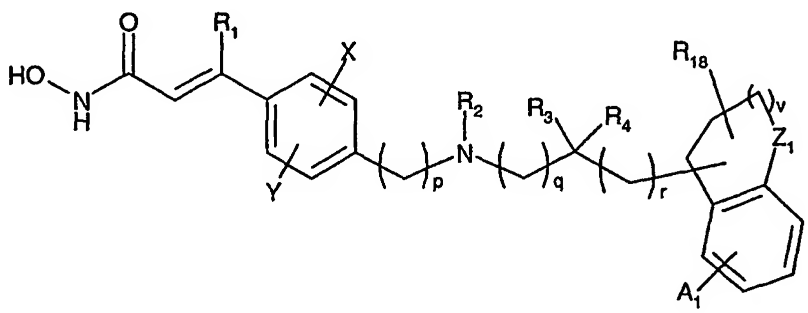
wherein

R_2' is selected from H, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, cycloalkylalkyl (e.g., cyclopropylmethyl), -$(CH_2)_{2\text{-}4}OR_{21}$ where R_{21} is H, methyl, ethyl, propyl, and *i*-propyl, and

R_5'' is unsubstituted 1*H*-indol-3-yl, benzofuran-3-yl or quinolin-3-yl, or substituted 1*H*-indol-3-yl, such as 5-fluoro-1*H*-indol-3-yl or 5-methoxy-1*H*-indol-3-yl, benzofuran-3-yl or quinolin-3-yl,

or a pharmaceutically acceptable salt thereof.

Another interesting genus of hydroxamate compounds are the compounds of formula Ic



(Ic)

wherein

the ring containing Z_1 is aromatic or non-aromatic, which non-aromatic rings are saturated or unsaturated,

Z_1 is O, S or N-R_{20},

R_{18} is H, halo, C_1-C_6alkyl (methyl, ethyl, t-butyl), C_3-C_7cycloalkyl, aryl, for example unsubstituted phenyl or phenyl substituted by 4-OCH_3 or 4-CF_3, or heteroaryl, such as 2-furanyl, 2-thiophenyl or 2-, 3- or 4-pyridyl;

R_{20} is H, C_1-C_6alkyl, C_1-C_6alkyl-C_3–C_9cycloalkyl (e.g., cyclopropylmethyl), aryl, heteroaryl, arylalkyl (e.g., benzyl), heteroarylalkyl (e.g., pyridylmethyl), acyl (acetyl, propionyl, benzoyl) or sulfonyl (methanesulfonyl, ethanesulfonyl, benzenesulfonyl, toluenesulfonyl);

A_1 is 1, 2 or 3 substituents which are independently H, C_1-C_6alkyl, -OR_{19}, halo, alkylamino, aminoalkyl, halo, or heteroarylalkyl (e.g., pyridylmethyl),

R_{19} is selected from H, C_1-C_6alkyl, C_4–C_9cycloalkyl, C_4–C_9heterocycloalkyl, aryl, heteroaryl, arylalkyl (e.g., benzyl), heteroarylalkyl (e.g., pyridylmethyl) and

$-(CH_2CH{=}CH(CH_3)(CH_2))_{1\text{-}3}H$;

R_2 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, amino acyl and $-(CH_2)_nR_7$;

v is 0, 1 or 2,

p is 0-3, and

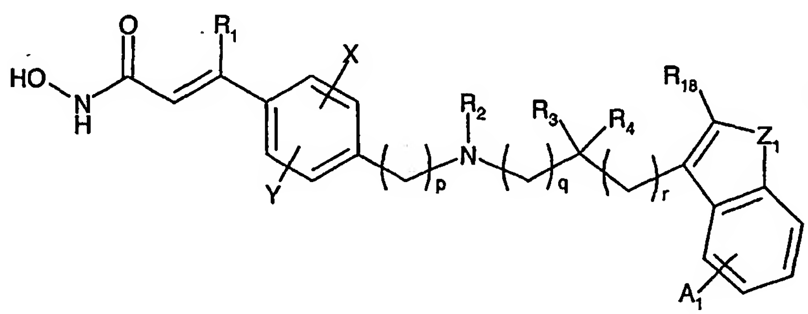
q is 1-5 and r is 0 or

q is 0 and r is 1-5,

or a pharmaceutically acceptable salt thereof. The other variable substituents are as defined above.

Especially useful compounds of formula Ic are those wherein R_2 is H, or $-(CH_2)_pCH_2OH$, wherein p is 1-3, especially those wherein R_1 is H; such as those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3, especially those wherein Z_1 is N-R_{20}. Among these compounds R_2 is preferably H or $-CH_2$-CH_2-OH and the sum of q and r is preferably 1.

Another interesting genus of hydroxamate compounds are the compounds of formula Id



(Id)

wherein

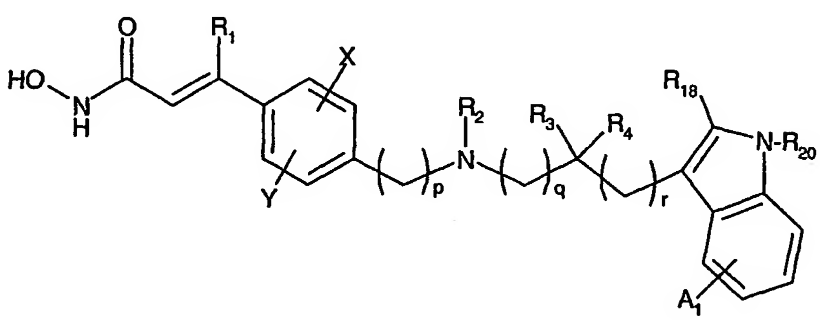
Z_1 is O, S or N-R_{20},

R_{18} is H, halo, C_1-C_6alkyl (methyl, ethyl, t-butyl), C_3-C_7cycloalkyl, aryl, for example, unsubstituted phenyl or phenyl substituted by 4-OCH_3 or 4-CF_3, or heteroaryl,

R_{20} is H, C_1-C_6alkyl, C_1-C_6alkyl-C_3–C_9cycloalkyl (e.g., cyclopropylmethyl), aryl, heteroaryl, arylalkyl (e.g., benzyl), heteroarylalkyl (e.g., pyridylmethyl), acyl (acetyl, propionyl, benzoyl) or sulfonyl (methanesulfonyl, ethanesulfonyl, benzenesulfonyl, toluenesulfonyl);
A_1 is 1, 2 or 3 substituents which are independently H, C_1-C_6alkyl, -OR_{19}, or halo,
R_{19} is selected from H, C_1-C_6alkyl, C_4–C_9cycloalkyl, C_4–C_9heterocycloalkyl, aryl, heteroaryl, arylalkyl (e.g., benzyl), and heteroarylalkyl (e.g., pyridylmethyl);
p is 0-3, and
q is 1-5 and r is 0 or
q is 0 and r is 1-5,
or a pharmaceutically acceptable salt thereof. The other variable substituents are as defined above.

Especially useful compounds of formula Id are those wherein R_2 is H, or -$(CH_2)_pCH_2OH$, wherein p is 1-3, especially those wherein R_1 is H; such as those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3. Among these compounds R_2 is preferably H or –CH_2-CH_2-OH and the sum of q and r is preferably 1.

The present invention further relates to compounds of the formula Ie



(Ie)

or a pharmaceutically acceptable salt thereof. The variable substituents are as defined above.

Especially useful compounds of formula Ie are those wherein R_{18} is H, fluoro, chloro, bromo, a C_1-C_4alkyl group, a substituted C_1-C_4alkyl group, a C_3-C_7cycloalkyl group, unsubstituted phenyl, phenyl substituted in the para position, or a heteroaryl (e.g., pyridyl) ring.

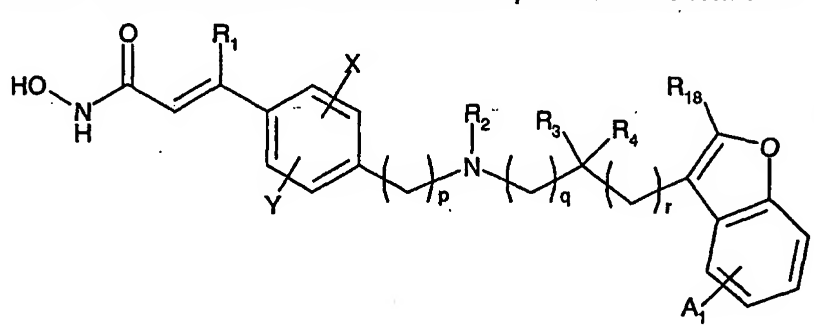
Another group of useful compounds of formula Ie are those wherein R_2 is H, or -$(CH_2)_pCH_2OH$, wherein p is 1-3, especially those wherein R_1 is H; such as those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3. Among these compounds R_2 is preferably H or $-CH_2-CH_2-OH$ and the sum of q and r is preferably 1.

Another group of useful compounds of formula Ie are those wherein R_{18} is H, methyl, ethyl, t-butyl, trifluoromethyl, cyclohexyl, phenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 2-furanyl, 2-thiophenyl, or 2-, 3- or 4-pyridyl wherein the 2-furanyl, 2-thiophenyl and 2-, 3- or 4-pyridyl substituents are unsubstituted or substituted as described above for heteroaryl rings; R_2 is H, or -$(CH_2)_pCH_2OH$, wherein p is 1-3; especially those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3. Among these compounds R_2 is preferably H or $-CH_2-CH_2-OH$ and the sum of q and r is preferably 1.

Those compounds of formula Ie wherein R_{20} is H or C_1-C_6alkyl, especially H, are important members of each of the subgenuses of compounds of formula Ie described above.

N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide and N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof, are important compounds of formula Ie.

The present invention further relates to the compounds of the formula If



(If)

or a pharmaceutically acceptable salt thereof. The variable substituents are as defined above.

Useful compounds of formula If are those wherein R_2 is H, or $-(CH_2)_pCH_2OH$, wherein p is 1-3, especially those wherein R_1 is H; such as those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3. Among these compounds R_2 is preferably H or $-CH_2-CH_2-OH$ and the sum of q and r is preferably 1.

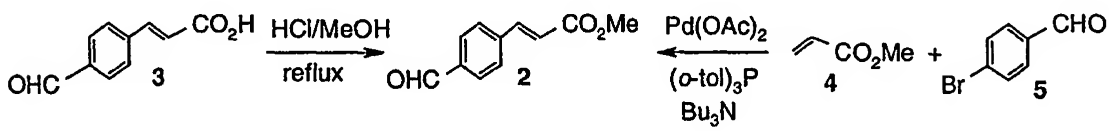
N-hydroxy-3-[4-[[[2-(benzofur-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide,or a pharmaceutically acceptable salt thereof, is an important compound of formula If.

The compounds described above are often used in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts include, when appropriate, pharmaceutically acceptable base addition salts and acid addition salts, for example, metal salts, such as alkali and alkaline earth metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts, and sulfonate salts. Acid addition salts include inorganic acid addition salts such as hydrochloride, sulfate and phosphate, and organic acid addition salts such as alkyl sulfonate, arylsulfonate, acetate, maleate, fumarate, tartrate, citrate and lactate. Examples of metal salts are alkali metal salts, such as lithium salt, sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt. Examples of ammonium salts are ammonium salt and tetramethylammonium salt. Examples of organic amine addition salts are salts with morpholine and piperidine. Examples of amino acid addition salts are salts with glycine, phenylalanine, glutamic acid and lysine. Sulfonate salts include mesylate, tosylate and benzene sulfonic acid salts.

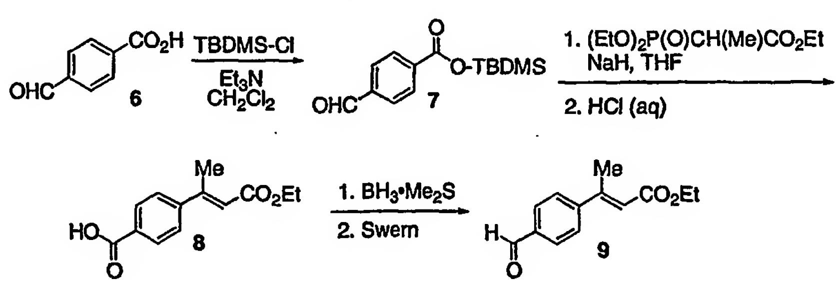
As is evident to those skilled in the art, the many of the deacetylase inhibitor compounds of the present invention contain asymmetric carbon atoms. It should be understood, therefore, that the individual stereoisomers are contemplated as being included within the scope of this invention.

The hydroxamate compounds of the present invention can be produced by known organic synthesis methods. For example, the hydroxamate compounds can be produced

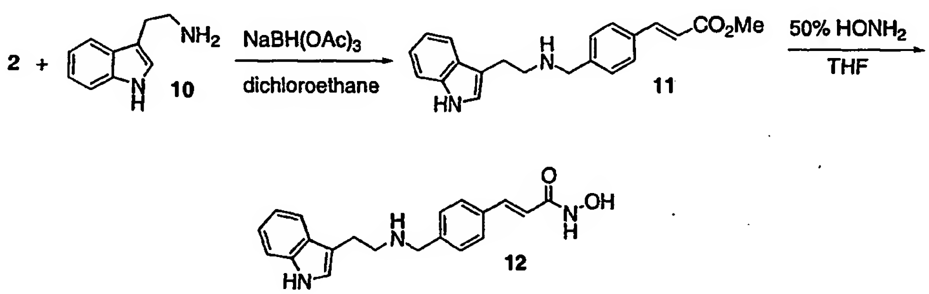
by reacting methyl 4-formyl cinnamate with tryptamine and then converting the reactant to the hydroxamate compounds. As an example, methyl 4-formyl cinnamate **2**, is prepared by acid catalyzed esterification of 4-formylcinnamic acid **3** (Bull. Chem. Soc. Jpn. 1995; 68:2355-2362). An alternate preparation of methyl 4-formyl cinnamate **2** is by a Pd-catalyzed coupling of methyl acrylate **4** with 4-bromobenzaldehyde **5**.



Additional starting materials can be prepared from 4-carboxybenzaldehyde **6**, and an exemplary method is illustrated for the preparation of aldehyde **9**, shown below. The carboxylic acid in 4-carboxybenzaldehyde **6** can be protected as a silyl ester (e.g., the *t*-butyldimethylsilyl ester) by treatment with a silyl chloride (e.g., *t*-butyldimethylsilyl chloride) and a base (e.g. triethylamine) in an appropriate solvent (e.g., dichloromethane). The resulting silyl ester **7** can undergo an olefination reaction (e.g., a Horner-Emmons olefination) with a phosphonate ester (e.g., triethyl 2-phosphonopropionate) in the presence of a base (e.g., sodium hydride) in an appropriate solvent (e.g., tetrahydrofuran (THF)). Treatment of the resulting diester with acid (e.g., aqueous hydrochloric acid) results in the hydrolysis of the silyl ester providing acid **8**. Selective reduction of the carboxylic acid of **8** using, for example, borane-dimethylsuflide complex in a solvent (e.g., THF) provides an intermediate alcohol. This intermediate alcohol could be oxidized to aldehyde **9** by a number of known methods, including, but not limited to, Swern oxidation, Dess-Martin periodinane oxidation, Moffatt oxidation and the like.

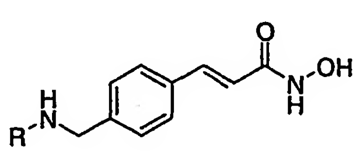


The aldehyde starting materials **2** or **9** can be reductively aminated to provide secondary or tertiary amines. This is illustrated by the reaction of methyl 4-formyl cinnamate **2** with tryptamine **10** using sodium triacetoxyborohydride ($NaBH(OAc)_3$) as the reducing agent in dichloroethane (DCE) as solvent to provide amine **11**. Other reducing agents can be used, e.g., sodium borohydride ($NaBH_4$) and sodium cyanoborohydride ($NaBH_3CN$), in other solvents or solvent mixtures in the presence or absence of acid catalysts (e.g., acetic acid and trifluoroacetic acid). Amine **11** can be converted directly to hydroxamic acid **12** by treatment with 50% aqueous hydroxylamine in a suitable solvent (e.g., THF in the presence of a base, e.g., NaOH). Other methods of hydroxamate formation are known and include reaction of an ester with hydroxylamine hydrochloride and a base (e.g., sodium hydroxide or sodium methoxide) in a suitable solvent or solvent mixture (e.g., methanol, ethanol or methanol/THF).

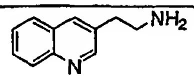
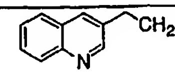
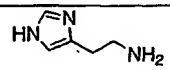
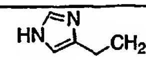
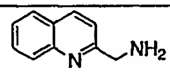
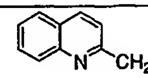
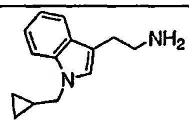
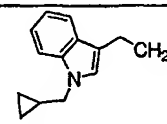
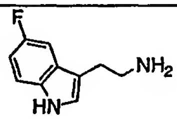
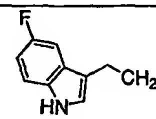
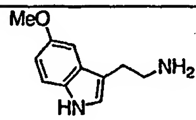
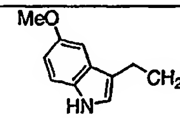
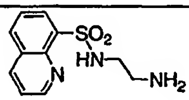
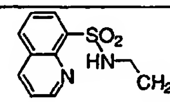
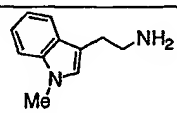
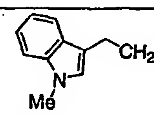
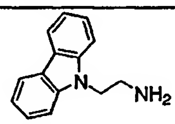
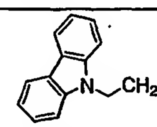


Aldehyde **2** can be reductively aminated with a variety of amines, exemplified by, but not limited to, those illustrated in Table 1. The resulting esters can be converted to target hydroxamates by the methods listed.

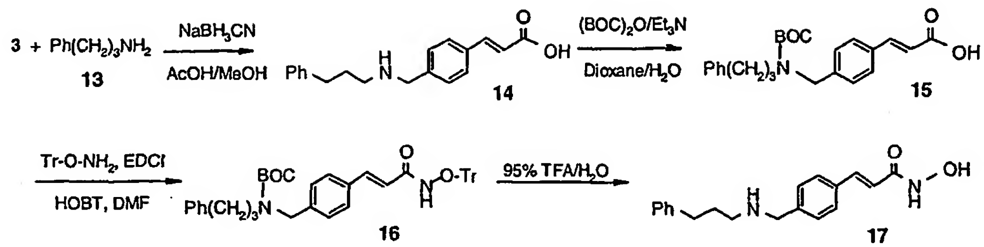
Table 1



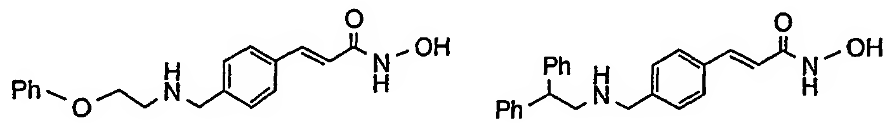
Amine	Reducing Conditions	Hydroxamate Conditions	R

	NaBH(OAc)$_3$ HOAc, DCE	2 M HONH$_2$ in MeOH	
	"	"	
	"	"	
	"	"	
	"	"	
	"	"	
	"	"	
	"	"	
	"	"	
Ph(CH$_2$)$_3$NH$_2$	NaBH$_3$CN/MeOH/ HOAc		Ph(CH$_2$)$_3$

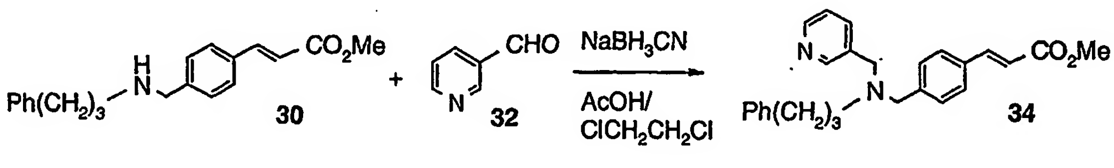
An alternate synthesis of the compounds of this invention starts by reductive amination of 4-formyl cinnamic acid **3**, illustrated below with 3-phenylpropylamine **13**, using, for example, NaBH$_3$CN as the reducing agent in MeOH and HOAc as a catalyst. The basic nitrogen of the resulting amino acid **14** can be protected, for example, as *t*-butoxycarbamate (BOC) by reaction with di-*t*-butyldicarbonate to give **15**.

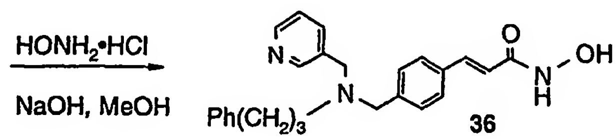


The carboxylic acid can be coupled with a protected hydroxylamine (e.g., *O*-trityl hydroxylamine) using a dehydrating agent (e.g., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI)) and a catalyst (e.g., 1-hydroxybenzotriazole hydrate (HOBT)) in a suitable solvent (e.g., DMF) to produce **16**. Treatment of **16** with a strong acid (e.g., trifluoroacetic acid (TFA)) provides a hydroxamic acid **17** of the present invention. Additional examples of compounds that can be prepared by this method are:



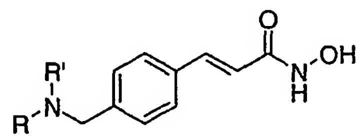
Tertiary amine compounds can be prepared by a number of methods. Reductive amination of **30** with nicotinaldehyde **32** using $NaBH_3CN$ as the reducing agent in dichloroethane and HOAc as a catalyst provides ester **34**. Other reducing agents can be used (e.g., $NaBH_4$ and $NaBH(OAc)_3$) in other solvents or solvent mixtures in the presence or absence of acid catalysts (e.g., acetic acid, trifluoroacetic acid and the like). Reaction of ester **34** with $HONH_2$•HCl, NaOH in MeOH provides hydroxamate **36**.



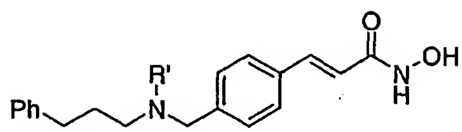


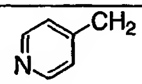
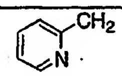
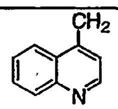
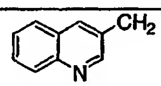
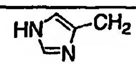
Tertiary amine compounds prepared by this methodology are exemplified, but not limited to, those listed in Table 2.

Table 2



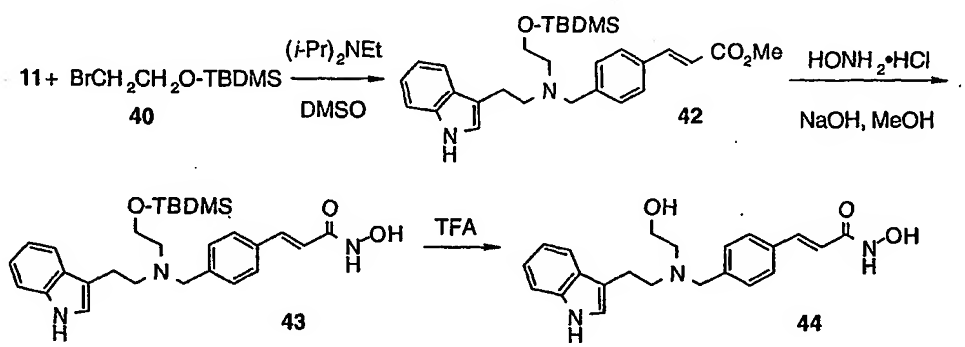
or



	Reducing Conditions	Hydroxamate Conditions
	$NaBH(OAc)_3$ HOAc, DCE	$HONH_2$•HCl/NaOMe/ MeOH
	$NaBH(OAc)_3$ HOAc, DCE	$HONH_2$•HCl/NaOMe/ MeOH
	$NaBH(OAc)_3$ HOAc, DCE	2 M $HONH_2$ in MeOH
	$NaBH_3CN$/MeOH/ HOAc	2 M $HONH_2$ in MeOH
	$NaBH(OAc)_3$ HOAc, DCE	2 M $HONH_2$ in MeOH

An alternate method for preparing tertiary amines is by reacting a secondary amine with an alkylating agent in a suitable solvent in the presence of a base. For example, heating a dimethylsulfoxide (DMSO) solution of amine **11** and bromide **40** in the presence of $(i\text{-}Pr)_2NEt$ yielded tertiary amine **42**. Reaction of the tertiary amine **42** with $HONH_2$•HCl, NaOH in MeOH provides hydroxamate **43**. The silyl group can be removed by any method

known to those skilled in the art. For example, the hydroxamate **43** can be treated with an acid, e.g., trifluoroacetic acid, or fluoride to produce hydroxyethyl compound **44**.



The hydroxamate compound, or salt thereof, is suitable for preparing pharmaceutical compositions, especially pharmaceutical compositions having deacetylase, especially histone deacetylase, inhibiting properties. Studies with athymic mice demonstrate that the hydroxamate compound causes HDA inhibition and increased histone acetylation *in vivo*, which triggers changes in gene expression that correlate with tumor growth inhibition.

The present invention further includes pharmaceutical compositions comprising a pharmaceutically effective amount of one or more of the above-described compounds as active ingredient. Pharmaceutical compositions according to the invention are suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, for the treatment of tumors, alone or in combination with one or more pharmaceutically acceptable carriers.

The hydroxamate compound is useful in the manufacture of pharmaceutical compositions having an effective amount the compound in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with (a) diluents; (b) lubricants, (c) binders (tablets); if desired, (d) disintegrants; and/or (e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants,

such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, the compositions may also contain other therapeutically valuable substances. The compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain preferably about 1 to 50% of the active ingredient.

Suitable formulations also include formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

As discussed above, the compounds of the present invention are useful for treating proliferative diseases. A proliferative disease is mainly a tumor disease (or cancer) (and/or any metastases). The inventive compounds are particularly useful for treating a tumor which is a breast cancer, genitourinary cancer, lung cancer, gastrointestinal cancer, epidermoid cancer, melanoma, ovarian cancer, pancreas cancer, neuroblastoma, head and/or neck cancer or bladder cancer, or in a broader sense renal, brain or gastric cancer; in particular (i) a breast tumor; an epidermoid tumor, such as an epidermoid head and/or neck tumor or a mouth tumor; a lung tumor, for example a small cell or non-small cell lung tumor; a gastrointestinal tumor, for example, a colorectal tumor; or a genitourinary tumor, for example, a prostate tumor (especially a hormone-refractory prostate tumor); or (ii) a proliferative disease that is refractory to the treatment with other chemotherapeutics; or (iii) a tumor that is refractory to treatment with other chemotherapeutics due to multidrug resistance.

In a broader sense of the invention, a proliferative disease may furthermore be a hyperproliferative condition such as leukemias, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis,

atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty.

Where a tumor, a tumor disease, a carcinoma or a cancer are mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis.

The compound is selectively toxic or more toxic to rapidly proliferating cells than to normal cells, particularly in human cancer cells, e.g., cancerous tumors, the compound has significant antiproliferative effects and promotes differentiation, e.g., cell cycle arrest and apoptosis. In addition, the hydroxamate compound induces p21, cyclin-CDK interacting protein, which induces either apoptosis or G1 arrest in a variety of cell lines.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereto.

Example P1

Preparation of *N*-Hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide.

4-formylcinnamic acid methylester is produced by adding 4-formylcinnamic acid (25 g, 0.143 mol) in MeOH and HCl (6.7 g, 0.18 mol). The resulting suspension is heated to reflux for 3 hours, cooled and evaporated to dryness. The resulting yellow solid is dissolved in EtOAc, the solution washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated to give a pale yellow solid which is used without further purification (25.0 g, 92%). To a solution of tryptamine (16.3 g, 100 mmol) and 4-formylcinnamic acid methylester (19 g, 100 mmol) in dichloroethane, $NaBH(OAc)_3$ (21 g, 100 mmol) is added. After 4 hours the mixture is diluted with 10% K_2CO_3 solution, the organic phase separated and the aqueous solution extracted with CH_2Cl_2. The combined organic extracts are dried (Na_2SO_4), evaporated and the residue purified by flash chromatography to produce 3-(4-{[2-(1*H*-indol-3-yl)-ethylamino]-methyl}-phenyl)-(2*E*)-2-propenoic acid methyl ester (29 g). A solution of KOH (12.9 g 87%, 0.2 mol) in MeOH (100 mL) is added to a solution of $HONH_2$•HCl (13.9 g, 0.2 mol) in MeOH (200 mL) and a precipitate results. After 15 minutes the mixture is filtered, the filter cake

washed with MeOH and the filtrate evaporated under vacuum to approximately 75 mL. The mixture is filtered and the volume adjusted to 100 mL with MeOH. The resulting solution 2M $HONH_2$ is stored under N_2 at –20° C for up to 2 weeks. Then 3-(4-{[2-(1*H*-indol-3-yl)-ethylamino]-methyl}-phenyl)-(2*E*)-2-propenoic acid methyl ester (2.20 g, 6.50 mmol) is added to 2 M $HONH_2$ in MeOH (30 mL, 60 mmol) followed by a solution of KOH (420 mg, 6.5 mmol) in MeOH (5 mL). After 2 hours dry ice is added to the reaction and the mixture is evaporated to dryness. The residue is dissolved in hot MeOH (20 mL), cooled and stored at –20 °C overnight. The resulting suspension is filtered, the solids washed with ice cold MeOH and dried under vacuum, producing *N*-Hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide (m/z 336 [MH^+]).

Example P2

Preparation of *N*-Hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide

A solution of 3-(4-{[2-(1*H*-indol-3-yl)-ethylamino]-methyl}-phenyl)-(2*E*)-2-propenoic acid methyl ester (12.6 g, 37.7 mmol), (2-bromoethoxy)-tert-butyldimethylsilane (12.8 g, 53.6 mmol), (i-Pr)$_2$NEt, (7.42 g, 57.4 mmol) in DMSO (100 mL) is heated to 50° C. After 8 hours the mixture is partitioned with CH_2Cl_2/H_2O. The organic layer is dried (Na_2SO_4) and evaporated. The residue is chromatographed on silica gel to produce 3-[4-({[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-[2-(1*H*-indol-3-yl)-ethyl]-amino}-methyl)-phenyl]-(2*E*)-2-propenoic acid methyl ester (13.1 g). Following the procedure described for the preparation of the hydroxamate compound in Example P1, 3-[4-({[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-[2-(1*H*-indol-3-yl)-ethyl]-amino}-methyl)-phenyl]-(2*E*)-2-propenoic acid methyl ester (5.4 g, 11 mmol) is converted to N-hydroxy-3-[4-({[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-[2-(1*H*-indol-3-yl)-ethyl]-amino}-methyl)-phenyl]-(2*E*)-2-propenamide (5.1 g;) and used without further purification. The hydroxamic acid (5.0 g, 13.3 mmol) is then dissolved in 95% TFA/H_2O (59 mL) and heated to 40 - 50 °C for 4 hours. The mixture is evaporated and the residue purified by reverse phase HPLC to produce *N*-Hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide as the trifluoroacetate salt (m/z 380 [MH^+]).

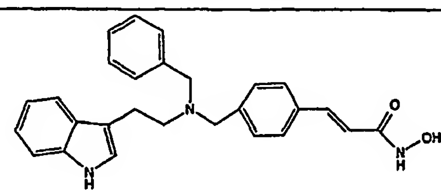
Example P3

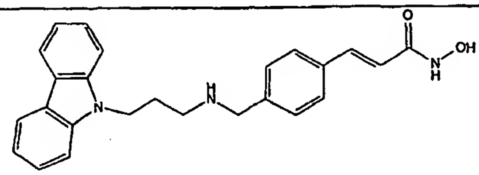
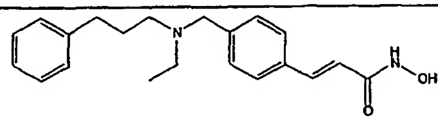
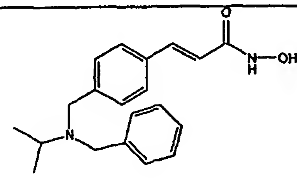
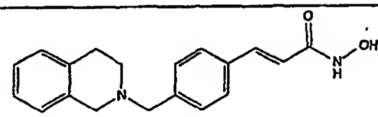
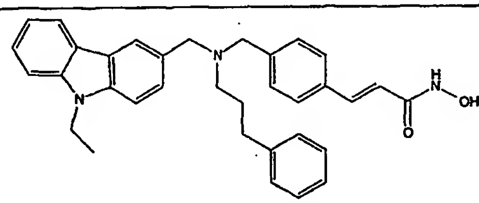
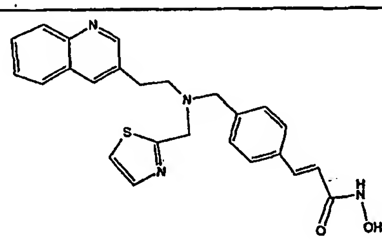
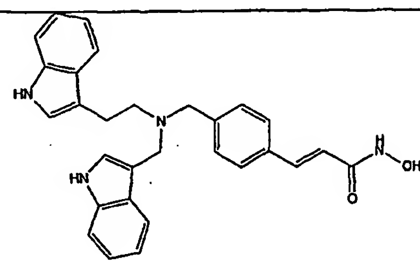
Preparation of N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide.

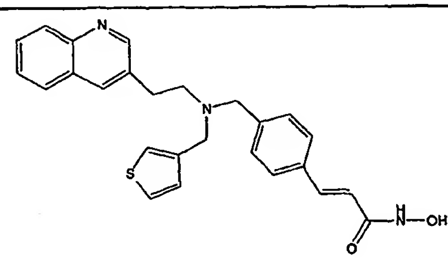
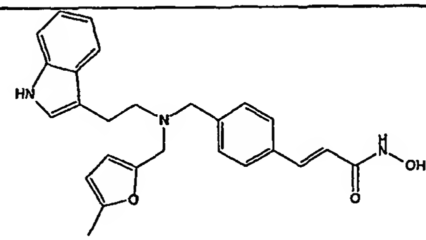
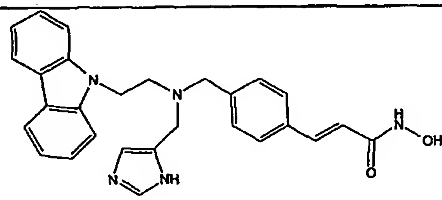
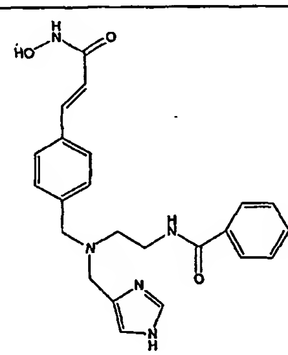
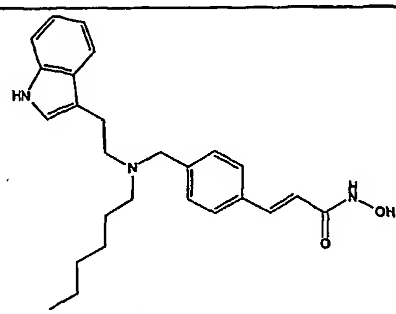
A suspension of $LiAlH_4$ (17 g, 445 mmol) in dry THF (1000 mL) is cooled to 0 °C and 2-methylindole-3-glyoxylamide (30 g, 148 mmol) is added in portions over 30 min. The mixture is stirred at room temperature for 30 min. and then maintained at reflux for 3 h. The reaction is cooled to 0 °C and treated with H_2O (17ml), 15% NaOH (aq., 17ml) and H_2O (51ml). The mixture is treated with $MgSO_4$, filtered and the filtrate evaporated to give 2-methyltryptamine which is dissolved in MeOH. Methyl 4-formylcinnamate (16.9 g, 88.8 mmol) is added to the solution, followed by $NaBH_3CN$ (8.4 g) and AcOH (1 equiv.). After 1h the reaction is diluted with $NaHCO_3$ (aq.) and extracted with EtOAc. The organic extracts are dried ($MgSO_4$), filtered and evaporated. The residue is purified by chromatography to give 3-(4-{[2-(2-methyl-1*H*-indol-3-yl)-ethylamino]-methyl}-phenyl)-(2*E*)-2-propenoic acid methyl ester. The ester is dissolved in MeOH, 1.0 M HCl/dioxane (1 – 1.5 equiv.) is added followed by Et_2O. The resulting precipitate is filtered and the solid washed with Et_2O and dried thoroughly to give 3-(4-{[2-(2-methyl-1*H*-indol-3-yl)-ethylamino]-methyl}-phenyl)-(2*E*)-2-propenoic acid methyl ester hydrochloride. 1.0 M NaOH (aq., 85 mL) is added to an ice cold solution of the methyl ester hydrochloride (14.9 g, 38.6 mmol) and $HONH_2$ (50% aq. solution, 24.0 mL, ca. 391.2 mmol). After 6 h, the ice cold solution is diluted with H_2O and NH_4Cl (aq., 0.86 M, 100 mL). The resulting precipitate is filtered, washed with H_2O and dried to afford N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide (m/z 350 [MH^+]).

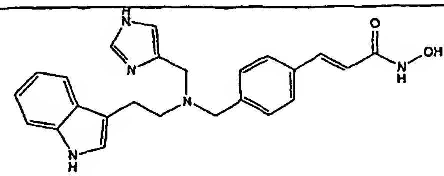
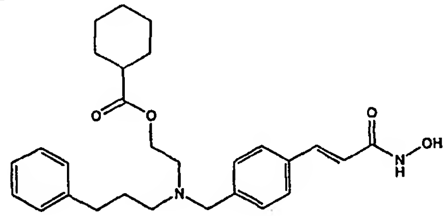
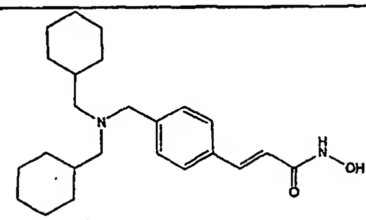
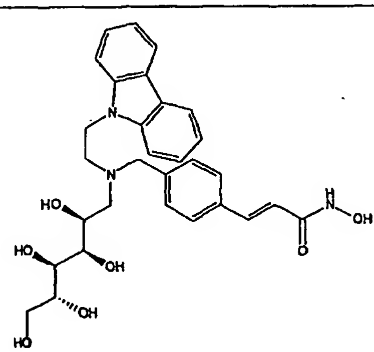
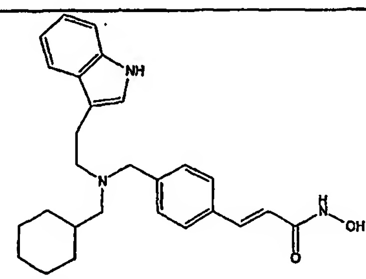
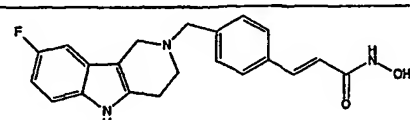
Examples 1-265

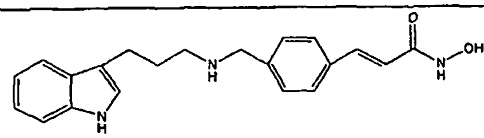
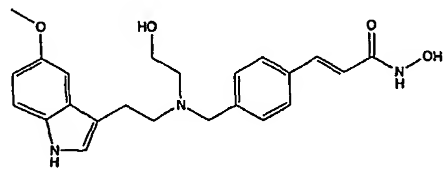
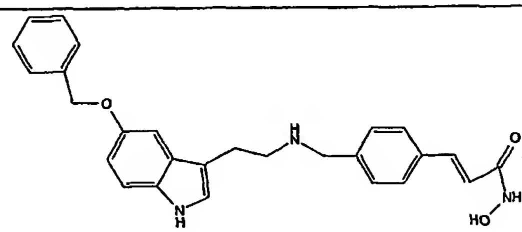
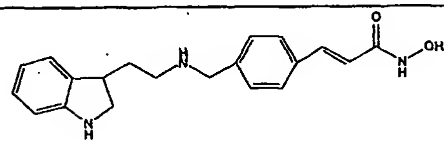
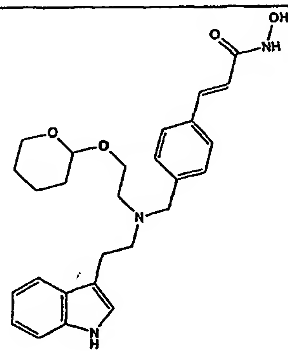
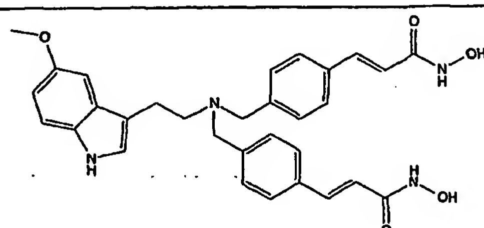
The following compounds are prepared by methods analogous to those disclosed in Examples P1, P2 and P3:

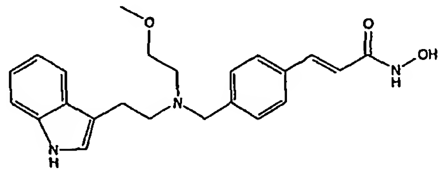
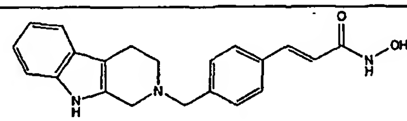
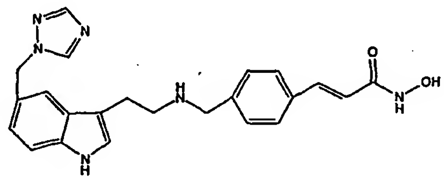
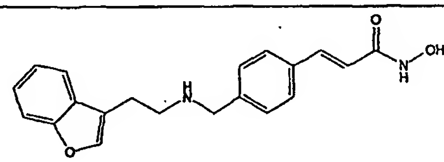
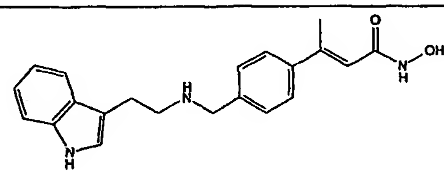
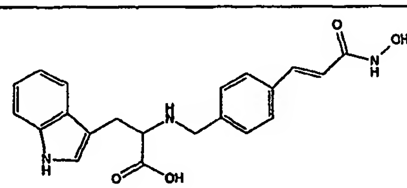
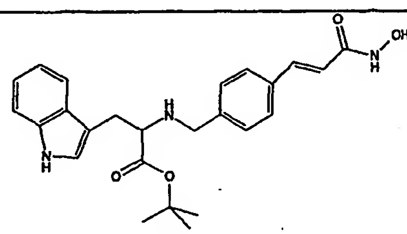
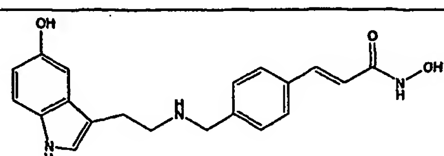
Example	STRUCTURE	m/z (MH^+)
1		426

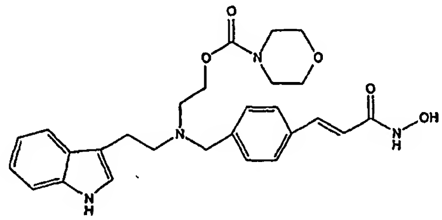
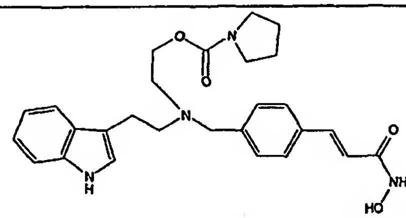
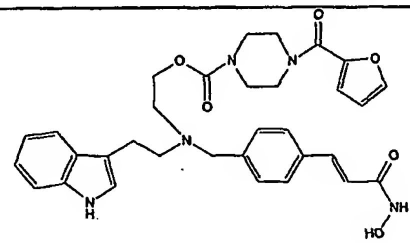
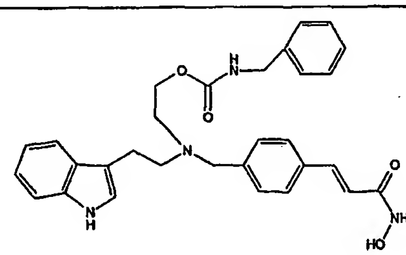
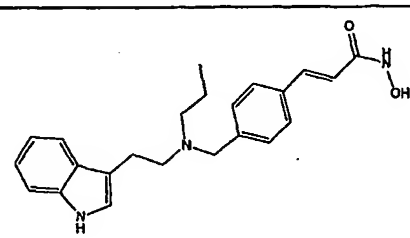
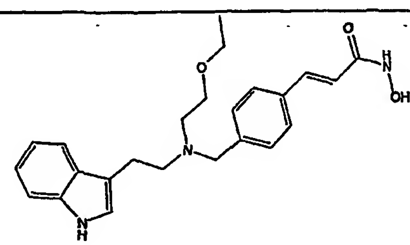
Example	STRUCTURE	m/z (MH$^+$)
2		
3		
4		325
5		
6		
7		
8		465

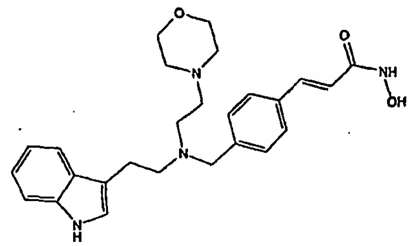
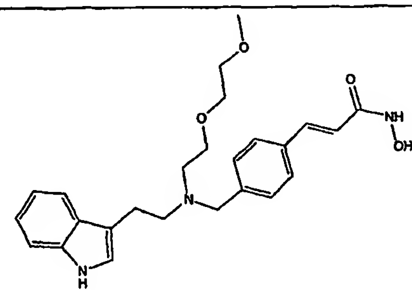
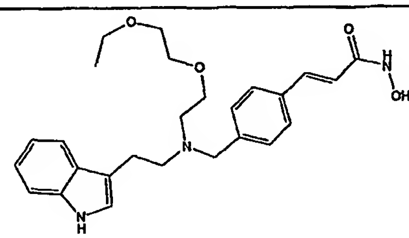
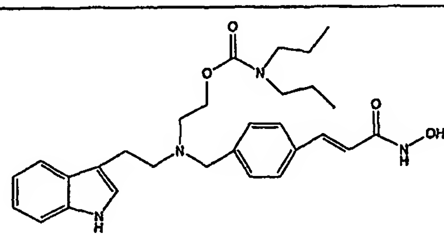
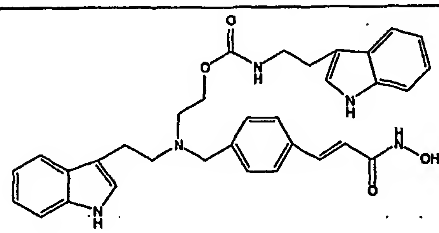
Example	STRUCTURE	m/z (MH^+)
9		
10		
11		
12		420
13		420

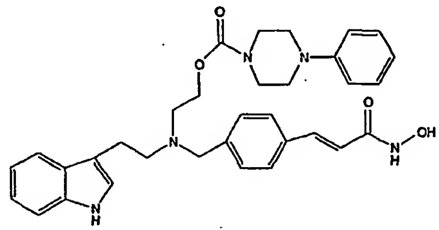
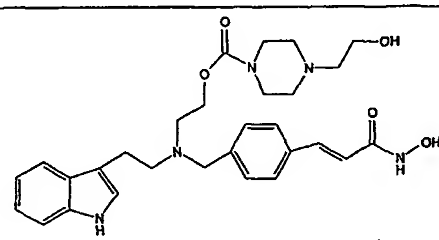
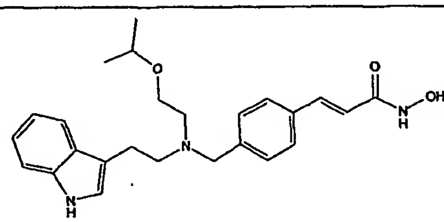
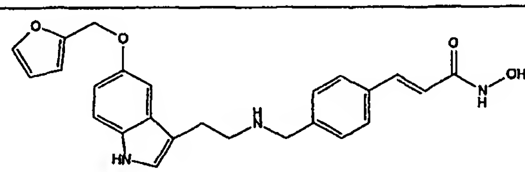
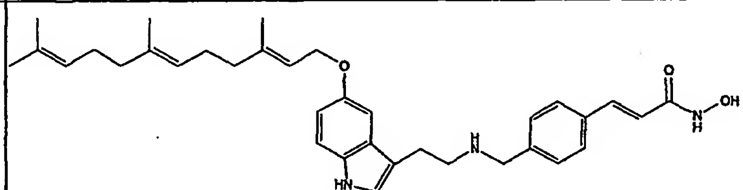
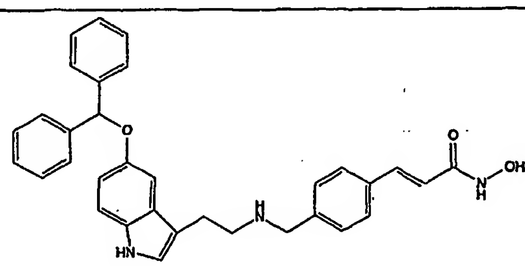
Example	STRUCTURE	m/z (MH+)
14		
15		465
16		385
17		550
18		432
19		366

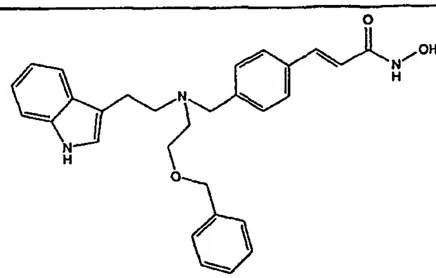
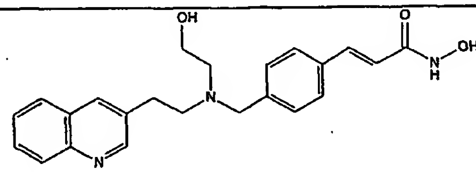
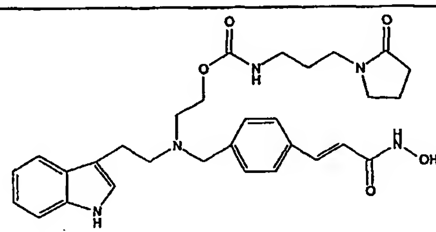
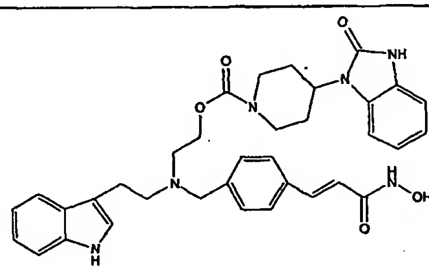
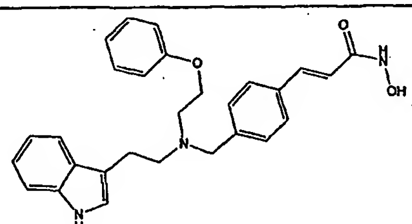
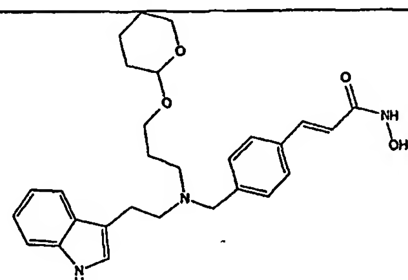
Example	STRUCTURE	m/z (MH⁺)
20		350
21		
22		442
23		338
24		464
25		541

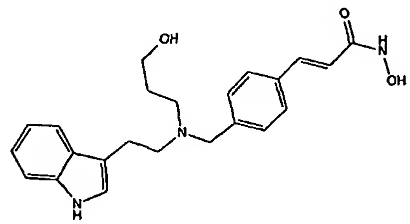
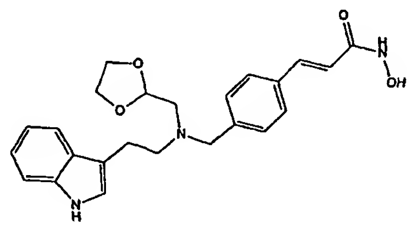
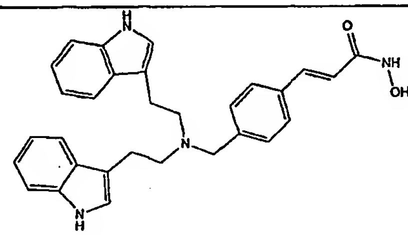
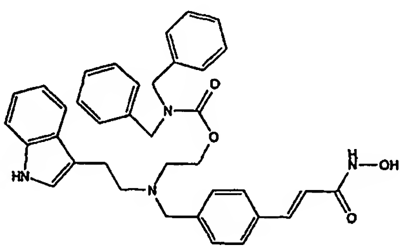
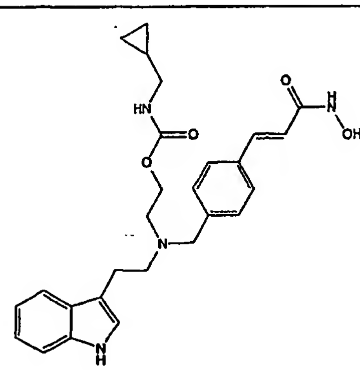
Example	STRUCTURE	m/z (MH⁺)
26		
27		
28		417
29		
30		
31		380
32		436
33		

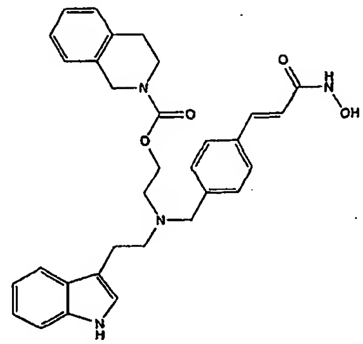
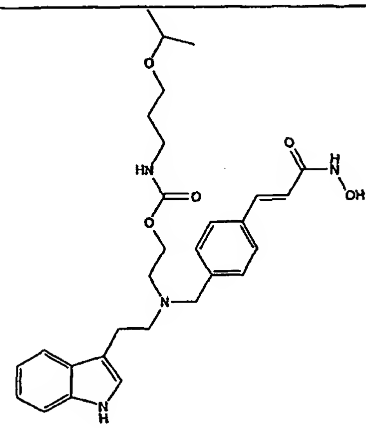
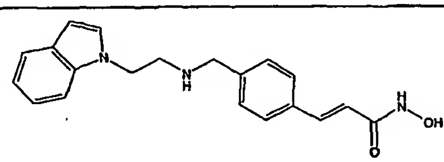
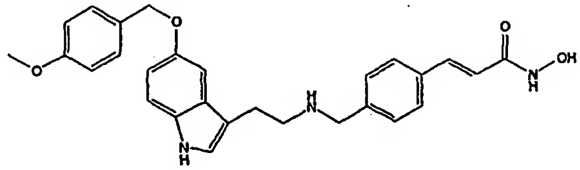
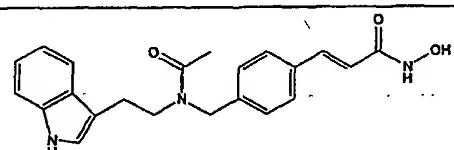
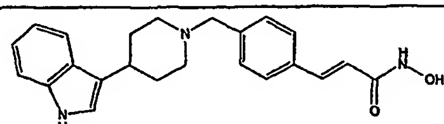
Example	STRUCTURE	m/z (MH⁺)
34		493
35		477
36		586
37		513
38		378
39		408

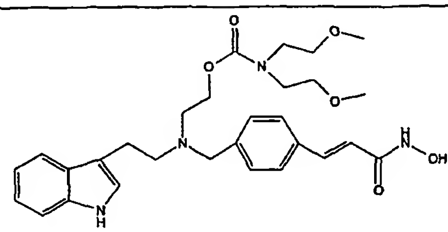
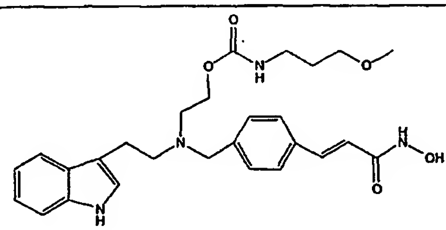
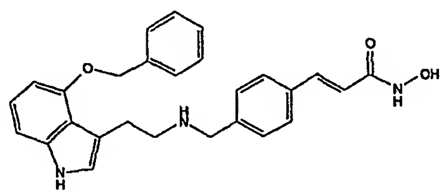
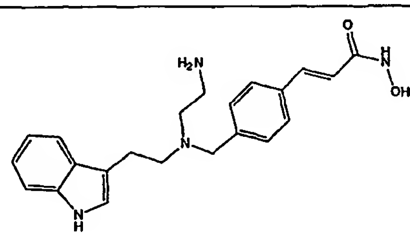
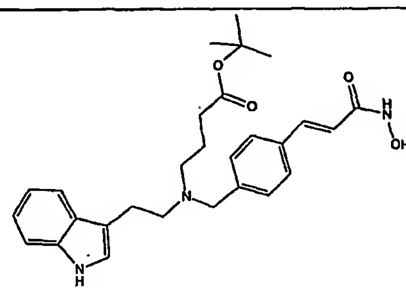
Example	STRUCTURE	m/z (MH+)
40		449
41		438
42		452
43		507
44		565

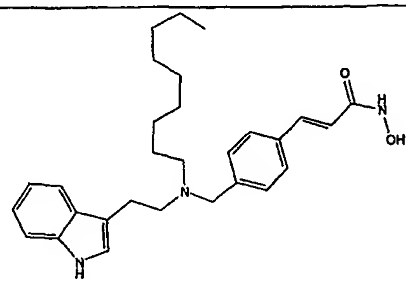
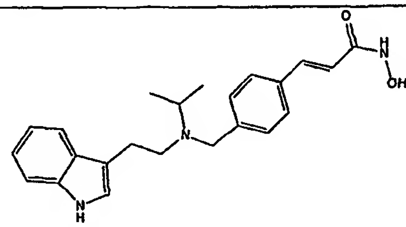
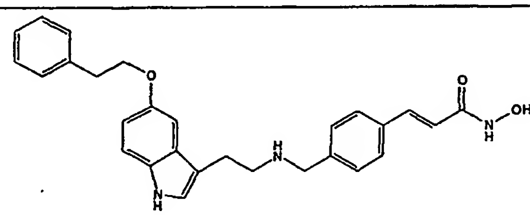
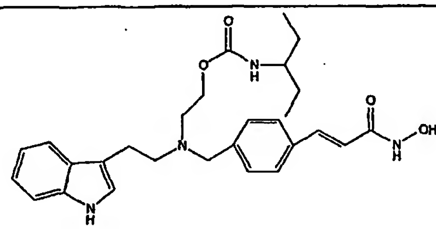
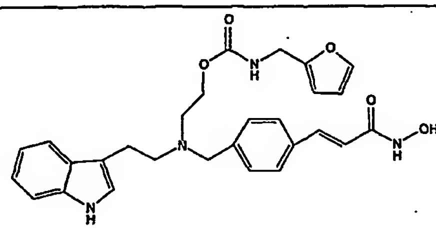
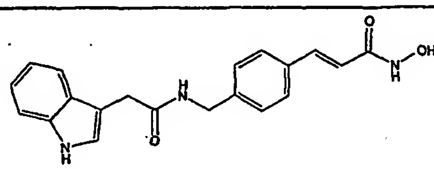
Example	STRUCTURE	m/z (MH⁺)
45		
46		
47		
48		
49		
50		

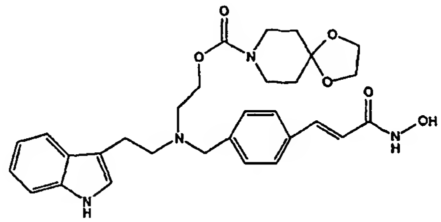
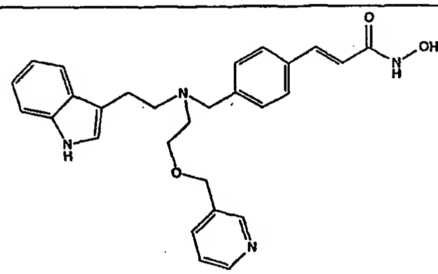
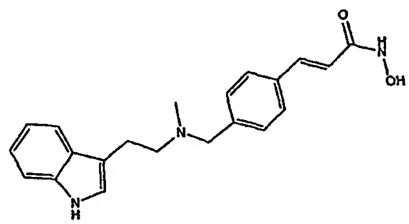
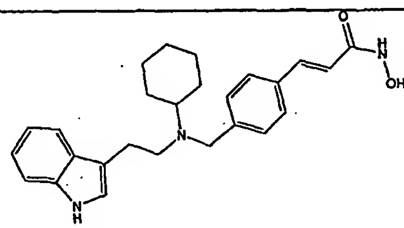
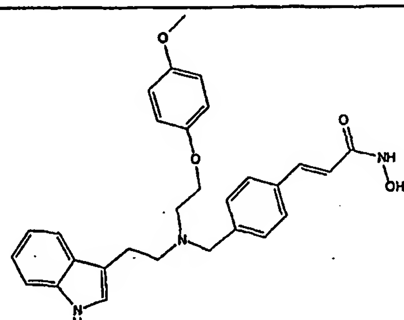
Example	STRUCTURE	m/z (MH⁺)
51		470
52		
53		548
54		623
55		456
56		478

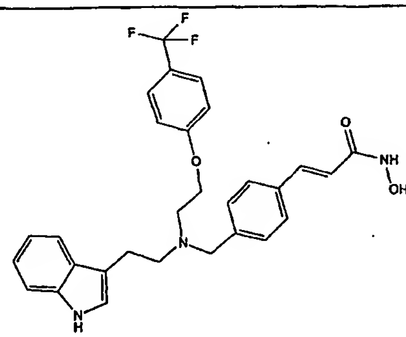
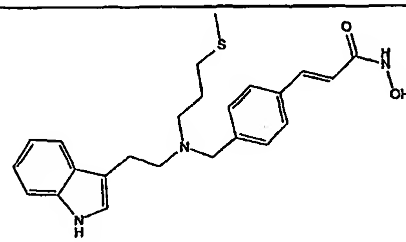
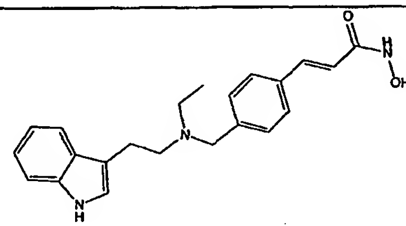
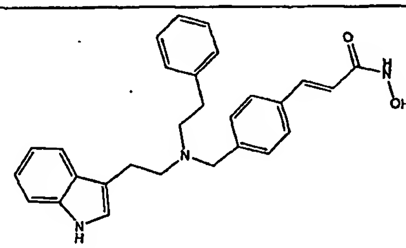
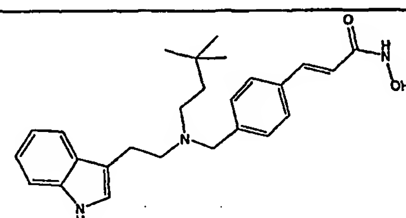
Example	STRUCTURE	m/z (MH+)
57		394
58		422
59		479
60		603
61		477

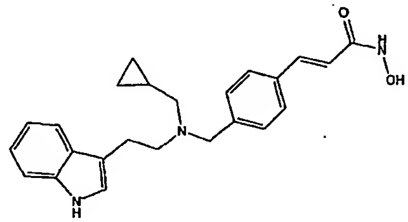
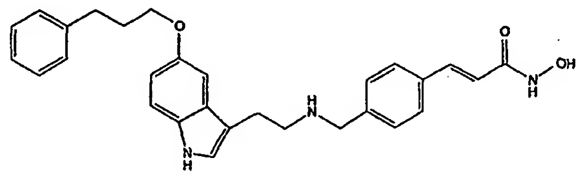
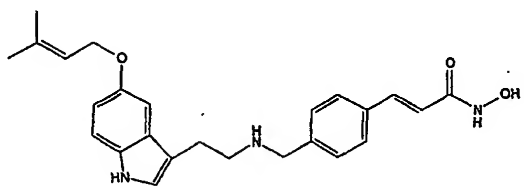
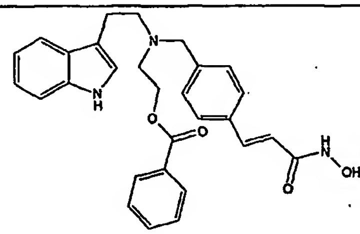
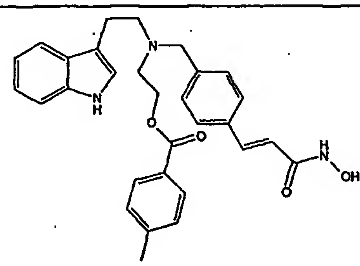
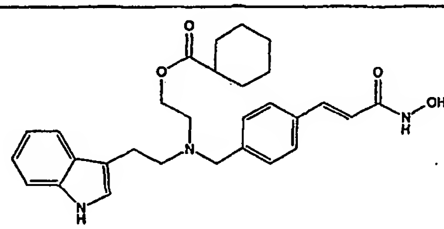
Example	STRUCTURE	m/z (MH+)
62		539
63		523
64		
65		
66		
67		

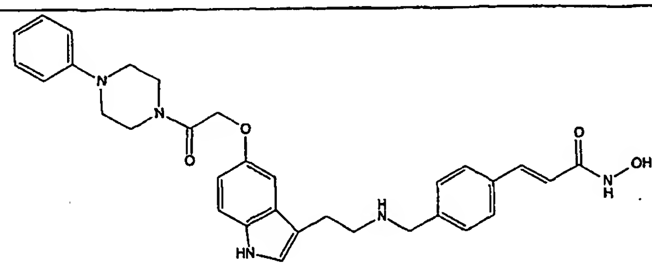
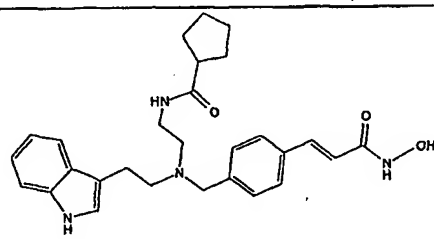
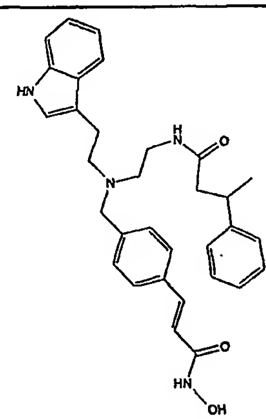
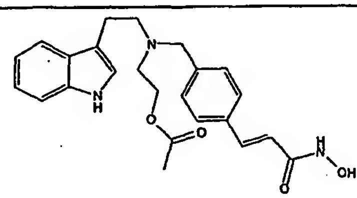
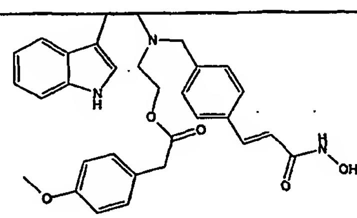
Example	STRUCTURE	m/z (MH$^+$)
68		539
69		495
70		
71		379
72		478

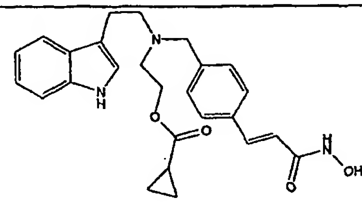
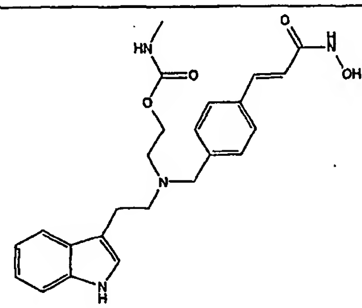
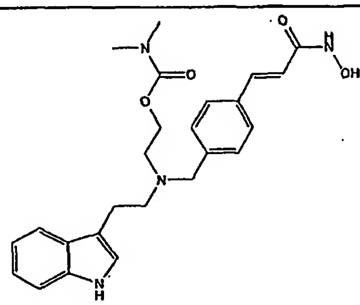
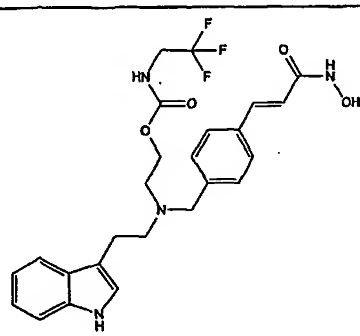
Example	STRUCTURE	m/z (MH$^+$)
73		462
74		378
75		
76		493
77		503
78		350

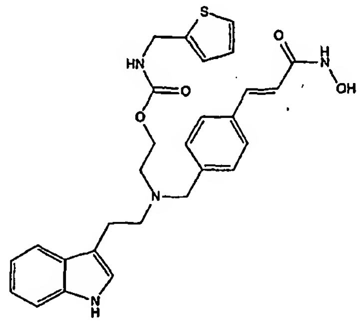
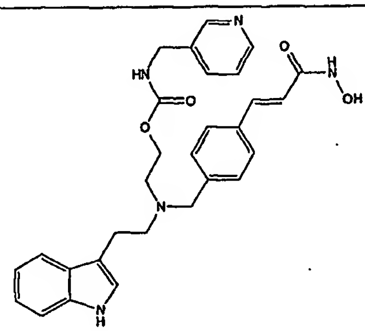
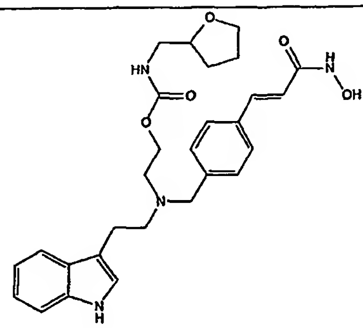
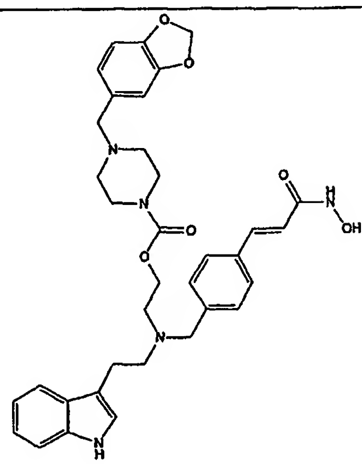
Example	STRUCTURE	m/z (MH⁺)
79		549
80		471
81		350
82		418
83		486

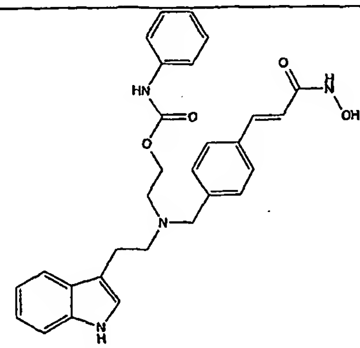
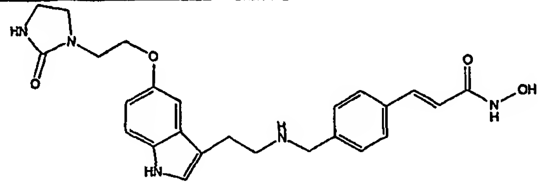
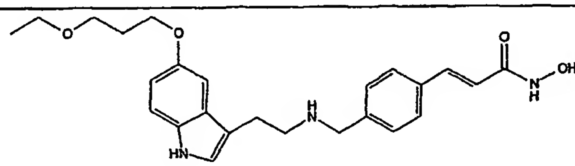
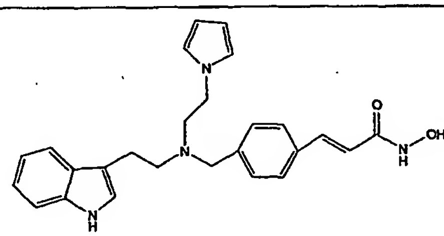
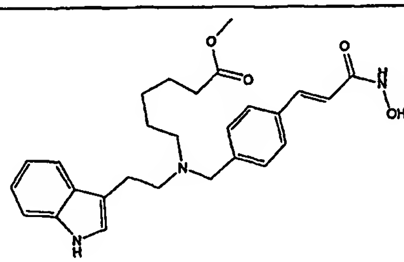
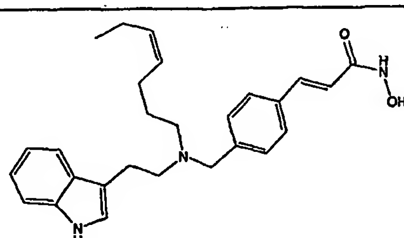
Example	STRUCTURE	m/z (MH⁺)
84		524
85		424
86		364
87		440
88		420

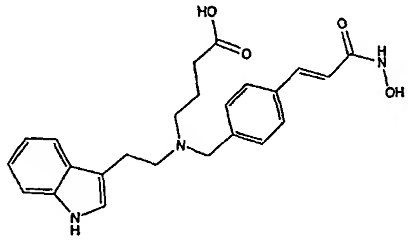
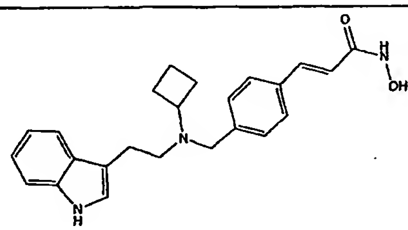
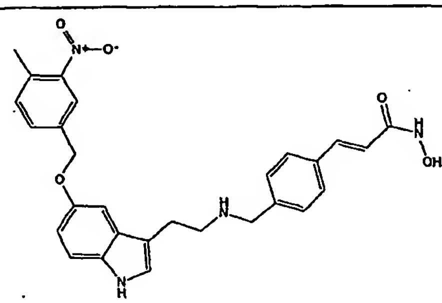
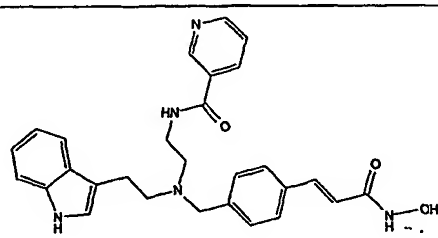
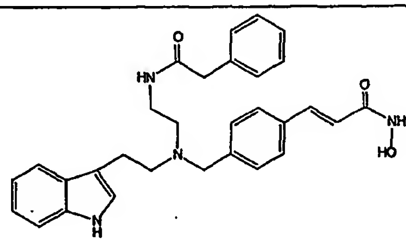
Example	STRUCTURE	m/z (MH⁺)
89		390
90		
91		
92		484
93		498
94		490

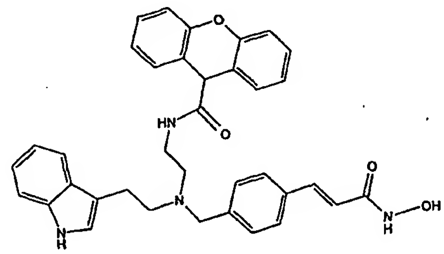
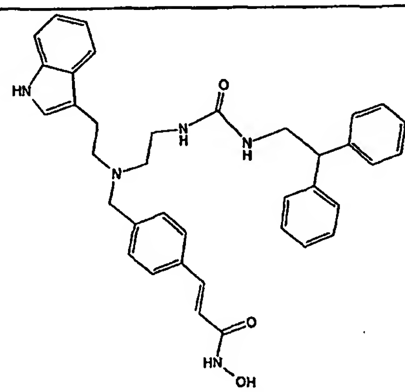
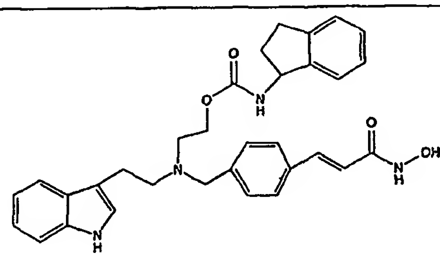
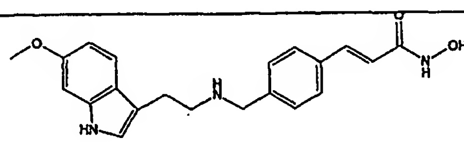
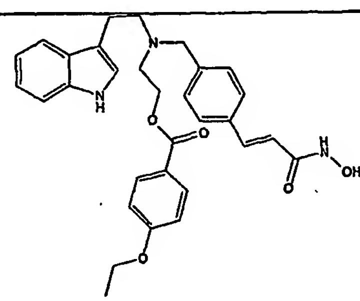
Example	STRUCTURE	m/z (MH^+)
95		
96		475
97		525
98		422
99		528

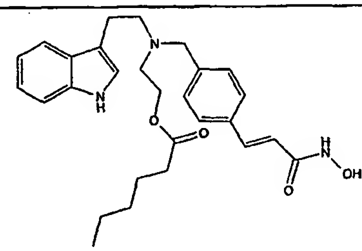
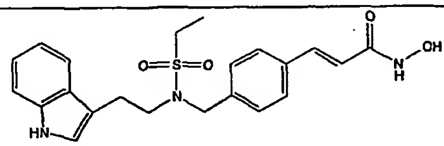
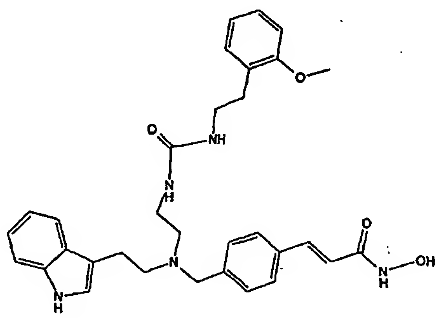
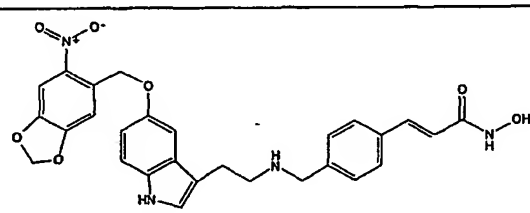
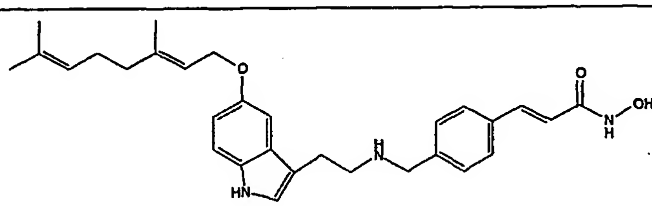
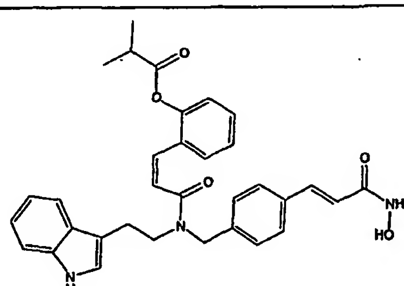
Example	STRUCTURE	m/z (MH^+)
100		448
101		437
102		451
103		505

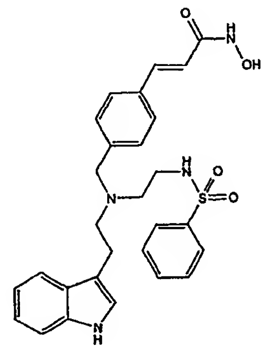
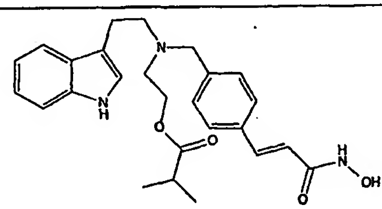
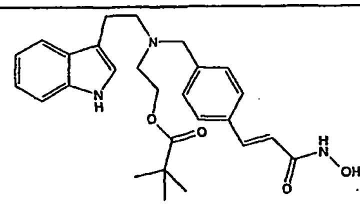
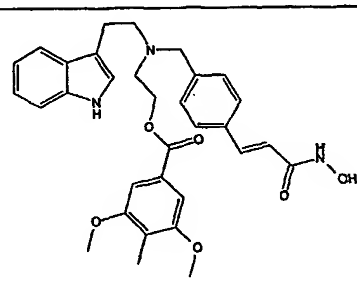
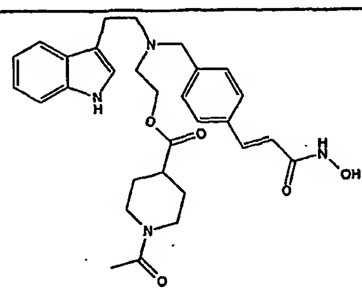
Example	STRUCTURE	m/z (MH⁺)
104		519
105		514
106		507
107		626

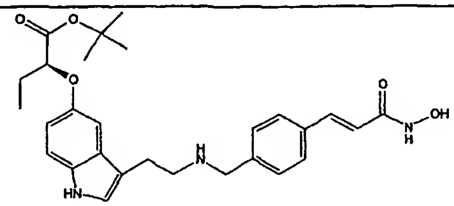
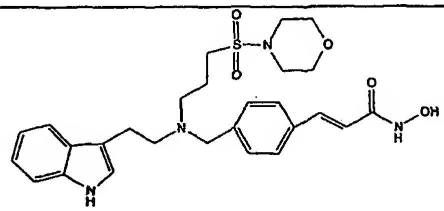
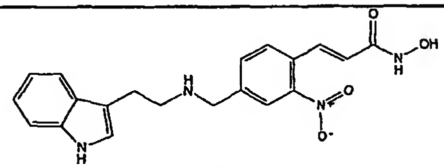
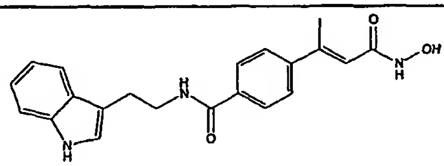
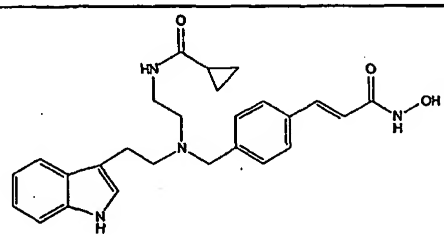
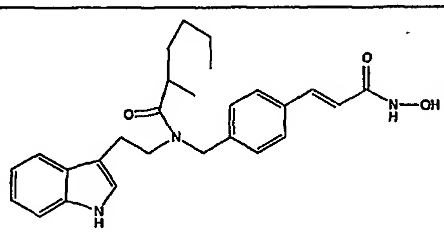
Example	STRUCTURE	m/z (MH$^+$)
108		499
109		
110		
111		429
112		464
113		432

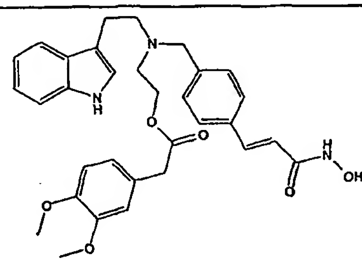
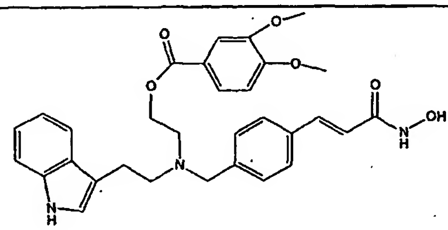
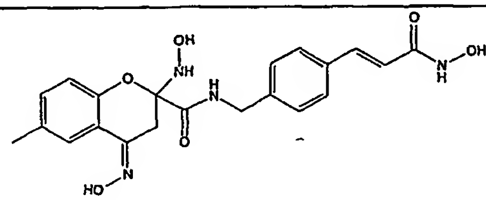
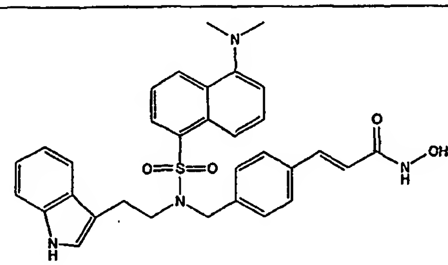
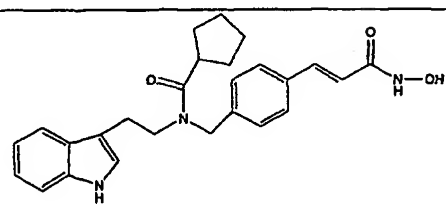
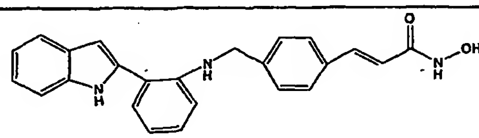
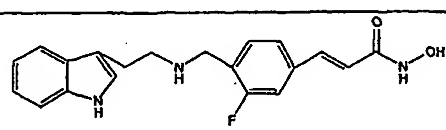
Example	STRUCTURE	m/z (MH⁺)
114		422
115		390
116		501
117		484
118		

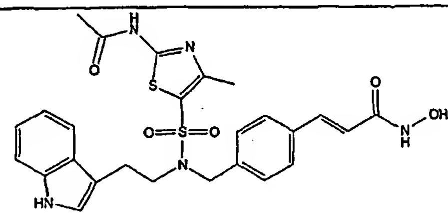
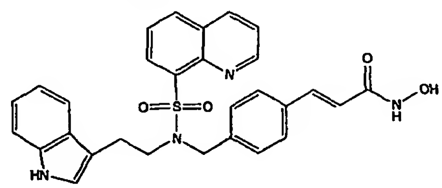
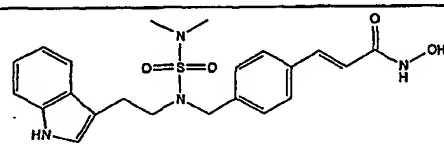
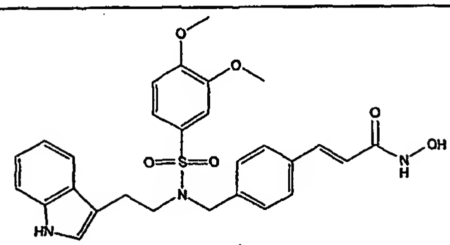
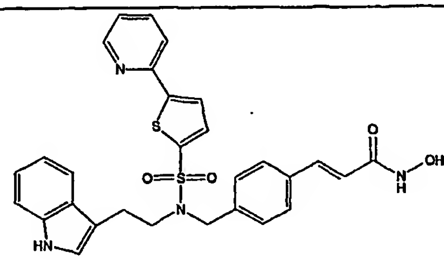
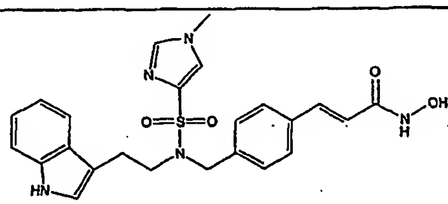
Example	STRUCTURE	m/z (MH$^+$)
119		587
120		602
121		539
122		
123		528

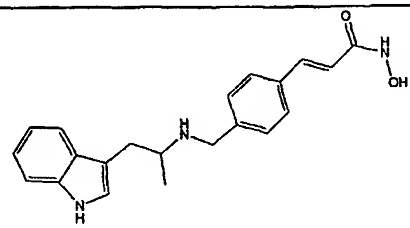
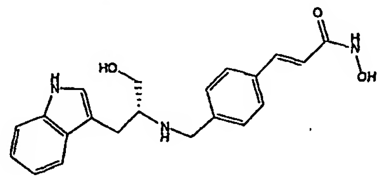
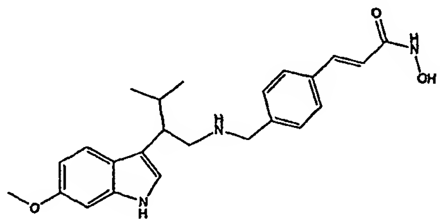
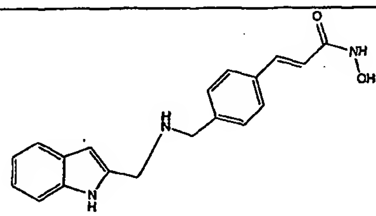
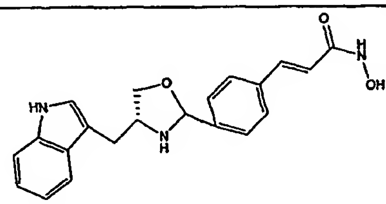
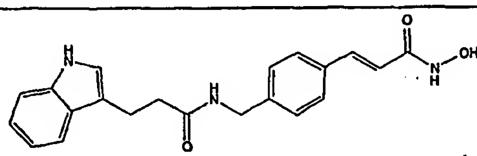
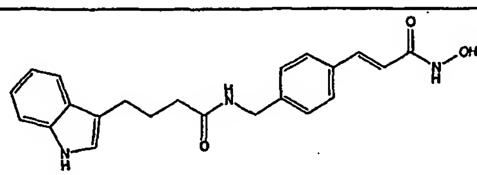
Example	STRUCTURE	m/z (MH$^+$)
124		487
125		
126		556
127		
128		
129		552

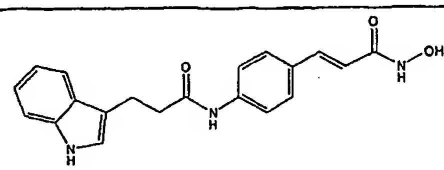
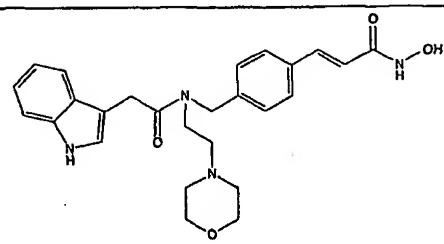
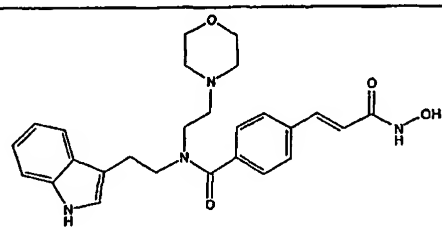
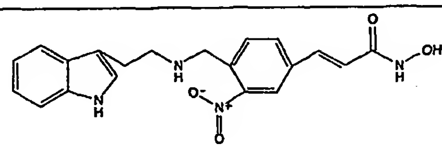
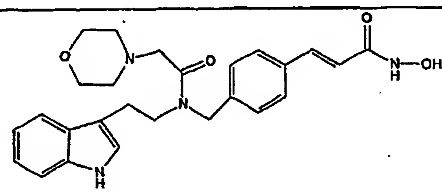
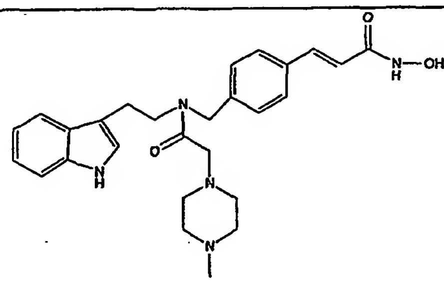
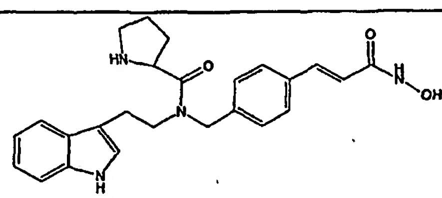
Example	STRUCTURE	m/z (MH⁺)
130		519
131		450
132		464
133		558
134		533

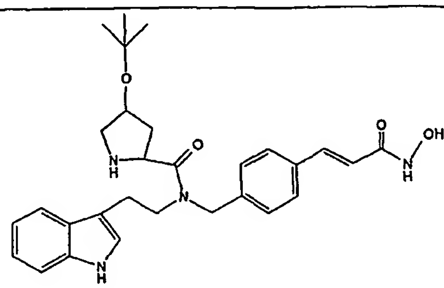
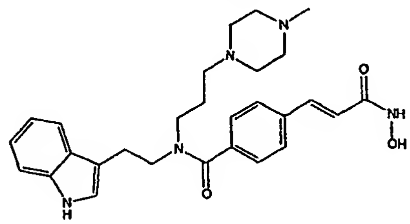
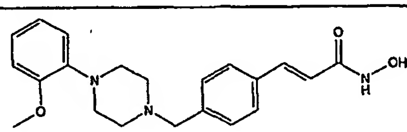
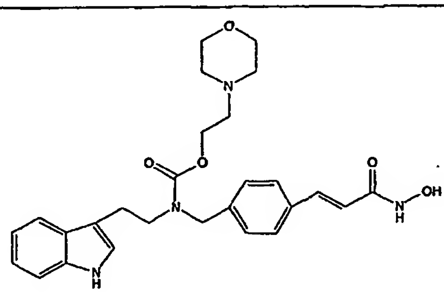
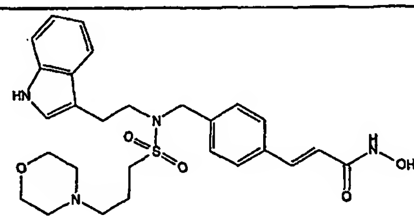
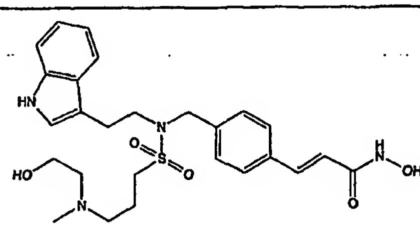
Example	STRUCTURE	m/z (MH⁺)
135		
136		527
137		381
138		364
139		
140		448

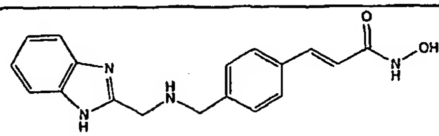
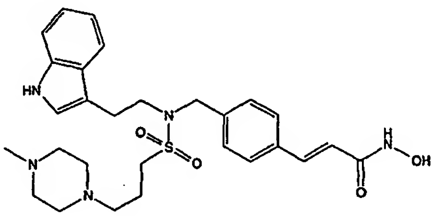
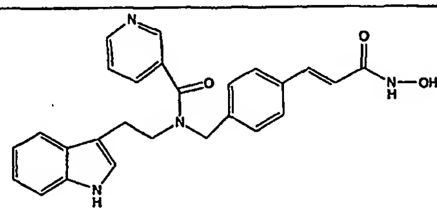
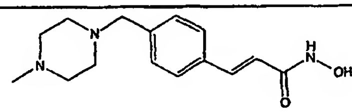
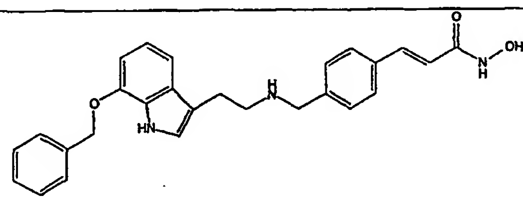
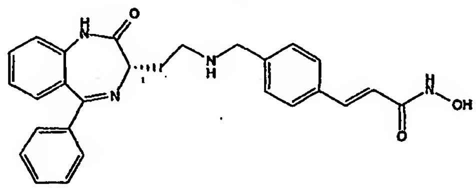
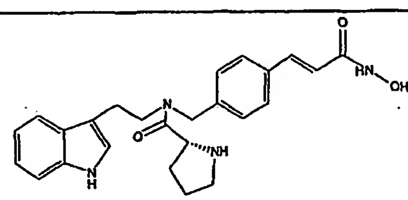
Example	STRUCTURE	m/z (MH+)
141		558
142		
143		427
144		
145		432
146		384
147		354

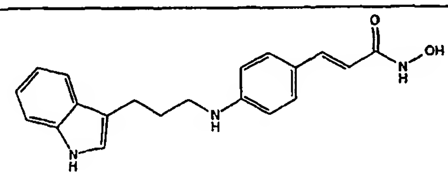
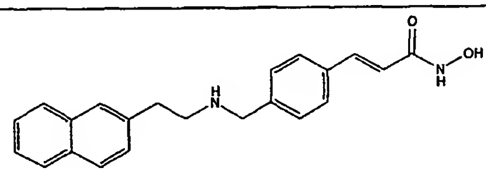
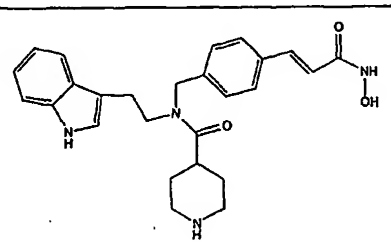
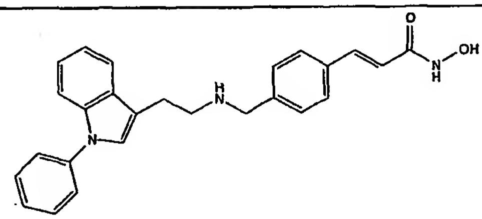
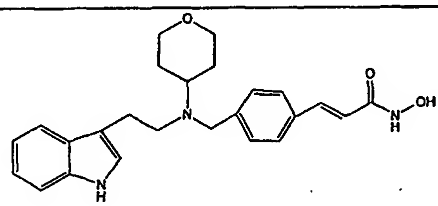
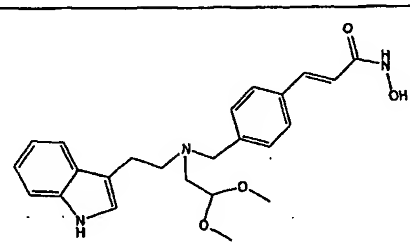
Example	STRUCTURE	m/z (MH+)
148		
149		
150		
151		
152		
153		

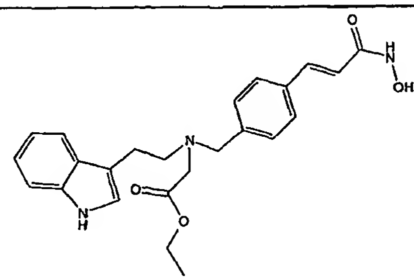
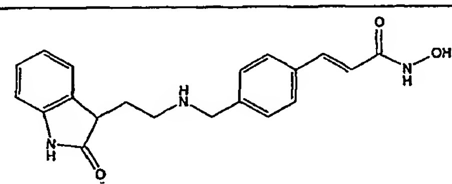
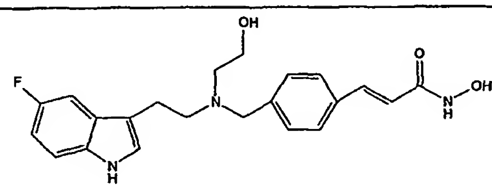
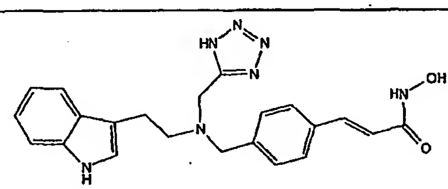
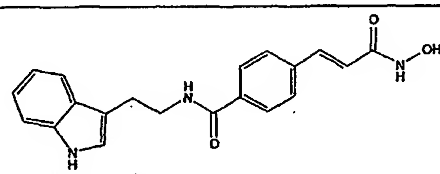
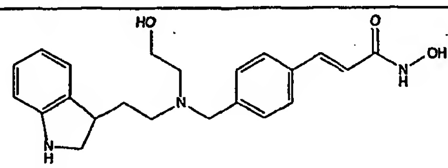
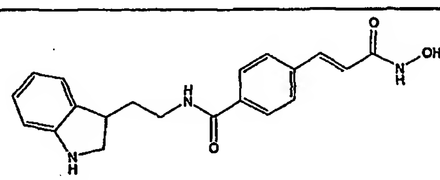
Example	STRUCTURE	m/z (MH⁺)
154		350
155		366
156		408
157		322
158		364
159		364
160		378

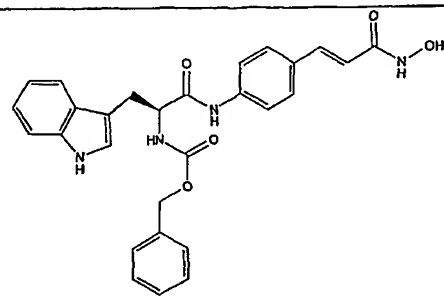
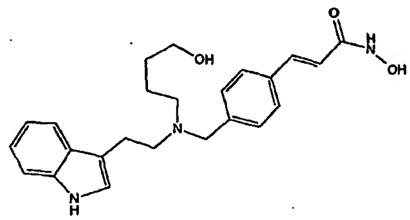
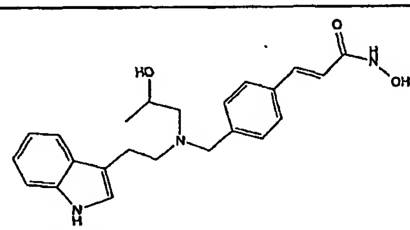
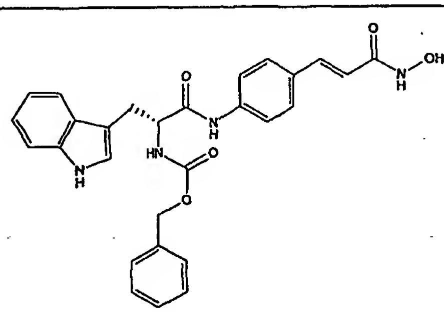
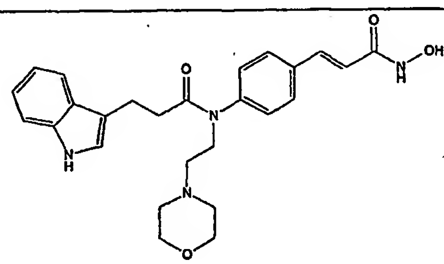
Example	STRUCTURE	m/z (MH⁺)
161		350
162		463
163		
164		381
165		463
166		476
167		

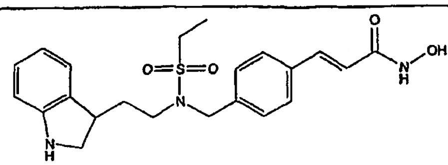
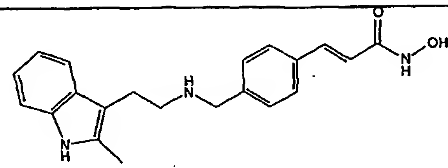
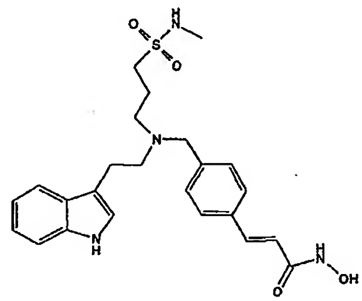
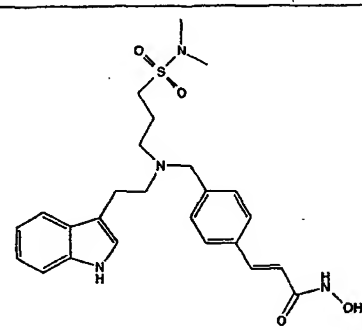
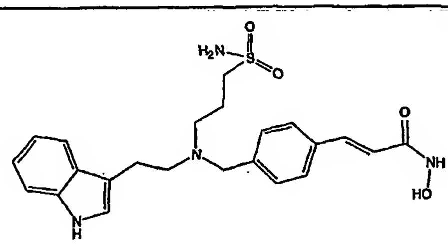
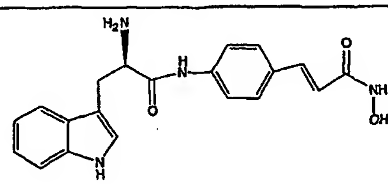
Example	STRUCTURE	m/z (MH⁺)
168		
169		
170		368
171		493
172		527
173		515

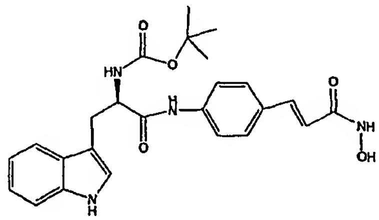
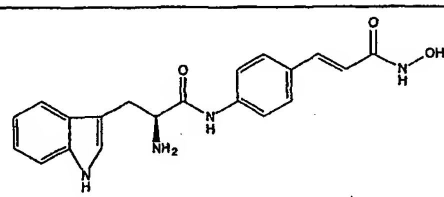
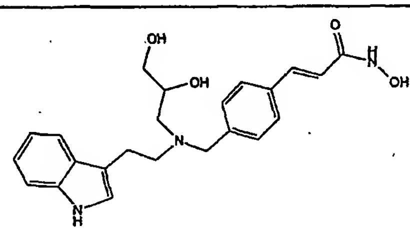
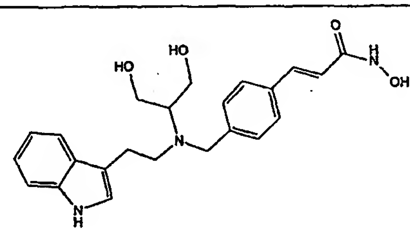
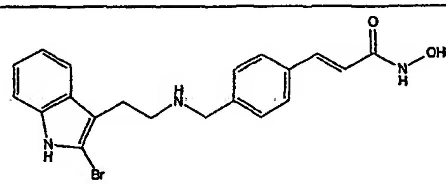
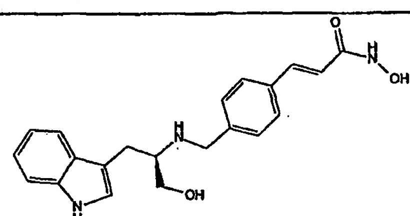
Example	STRUCTURE	m/z (MH^+)
174		323
175		540
176		441
177		276
178		
179		455
180		

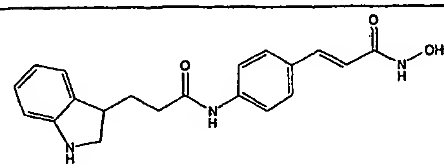
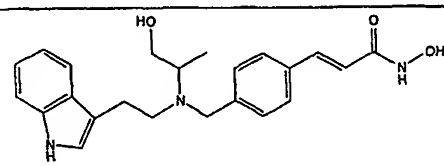
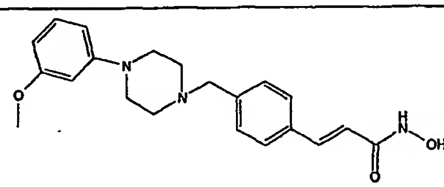
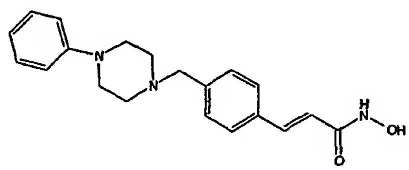
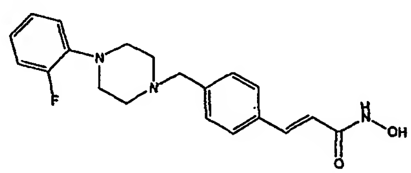
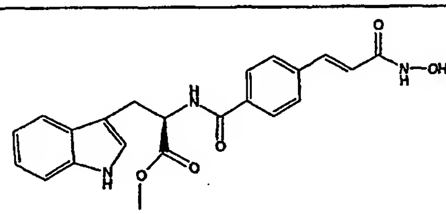
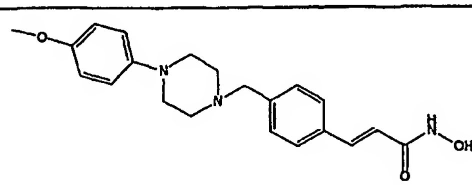
Example	STRUCTURE	m/z (MH⁺)
181		336
182		347
183		447
184		
185		420
186		424

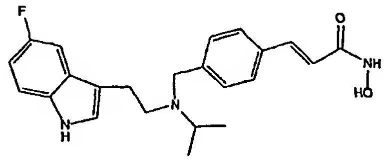
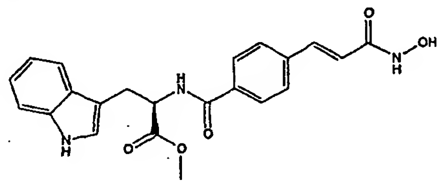
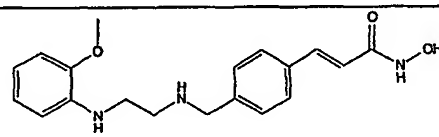
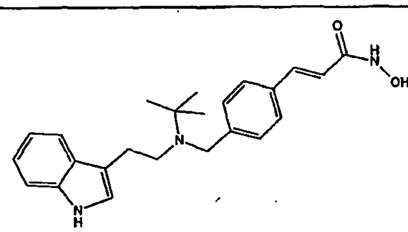
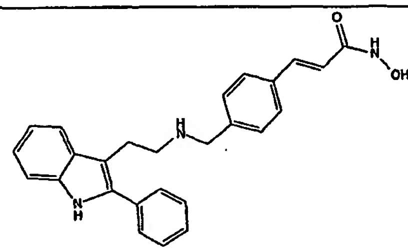
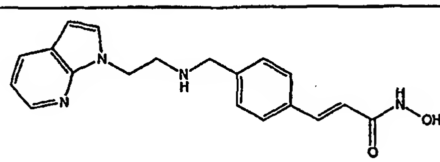
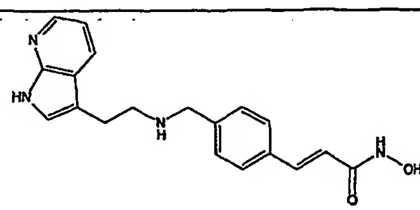
Example	STRUCTURE	m/z (MH+)
187		422
188		
189		398
190		418
191		350
192		
193		352

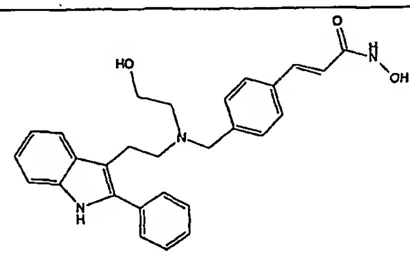
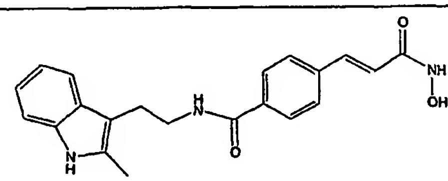
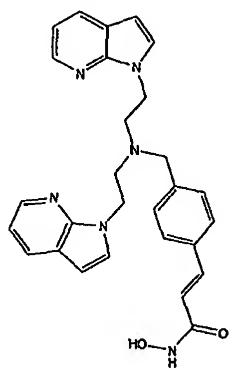
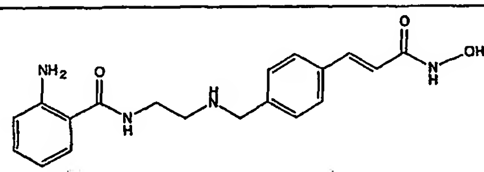
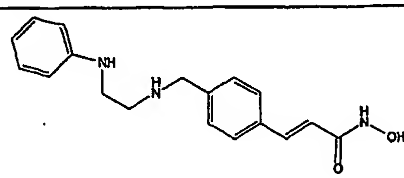
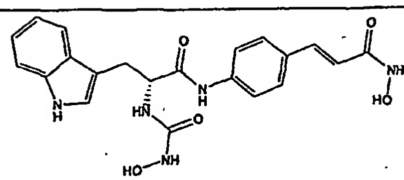
Example	STRUCTURE	m/z (MH⁺)
194		499
195		408
196		394
197		499
198		

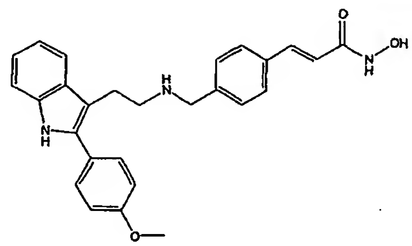
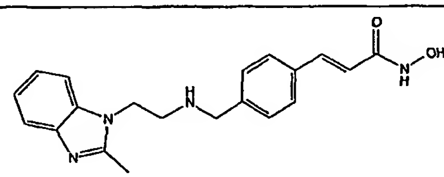
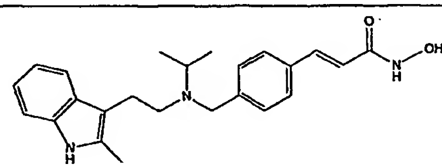
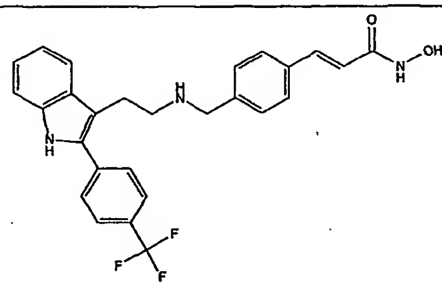
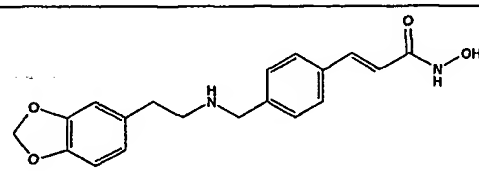
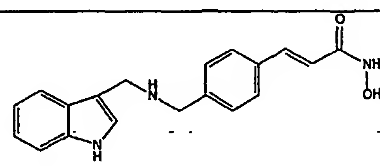
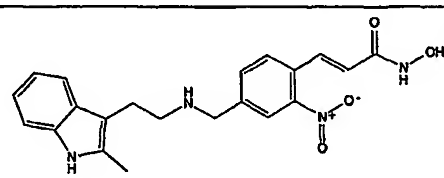
Example	STRUCTURE	m/z (MH⁺)
199		
200		350
201		
202		
203		
204		365

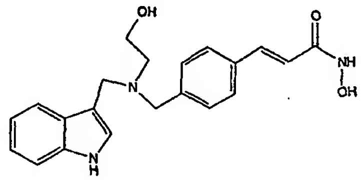
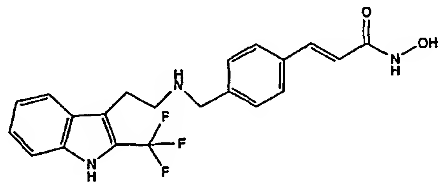
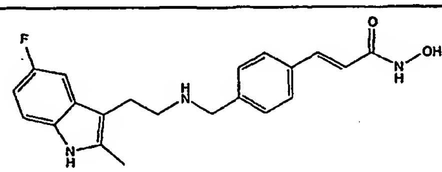
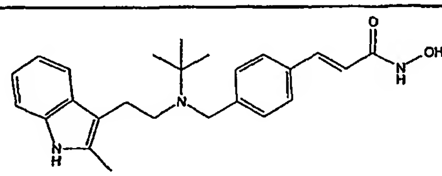
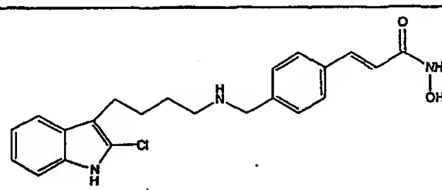
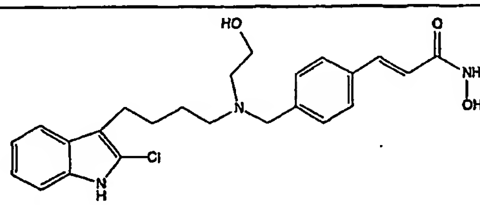
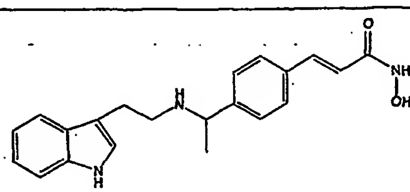
Example	STRUCTURE	m/z (MH⁺)
205		465
206		
207		410
208		410
209		
210		366

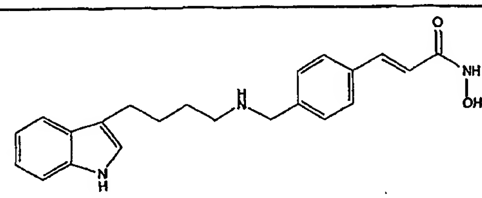
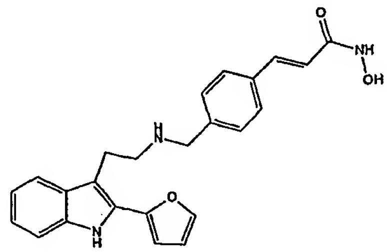
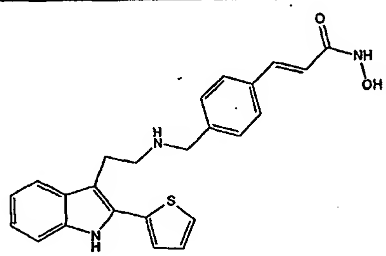
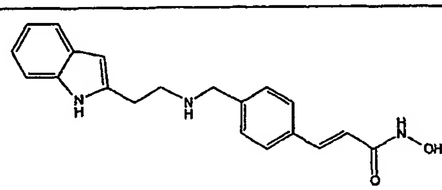
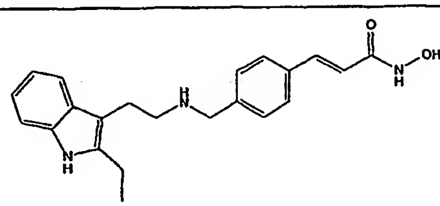
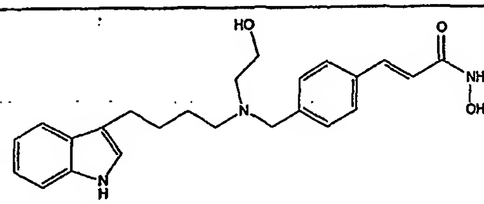
Example	STRUCTURE	m/z (MH⁺)
211		352
212		
213		368
214		338
215		356
216		408
217		368

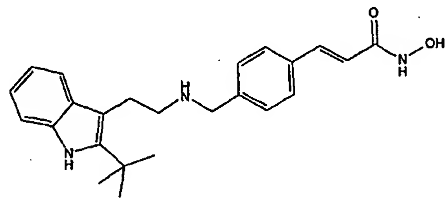
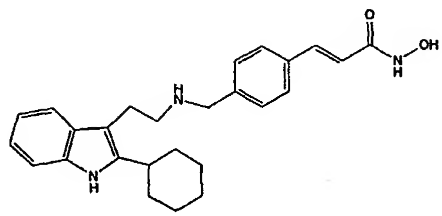
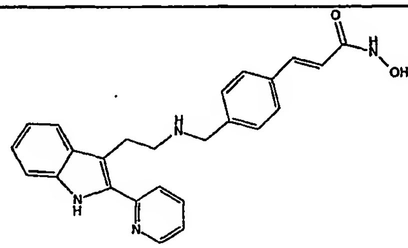
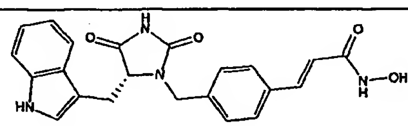
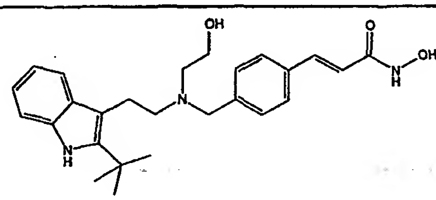
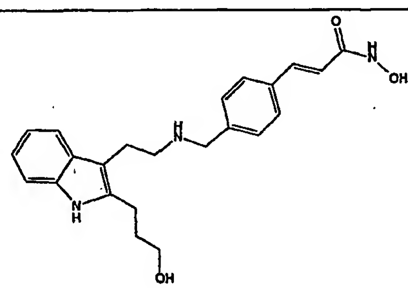
Example	STRUCTURE	m/z (MH+)
218		396
219		
220		342
221		392
222		412
223		337
224		337

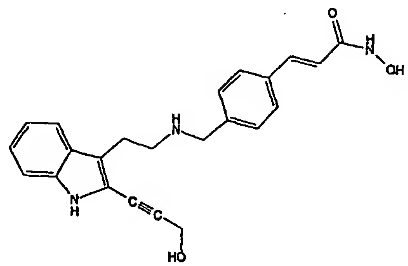
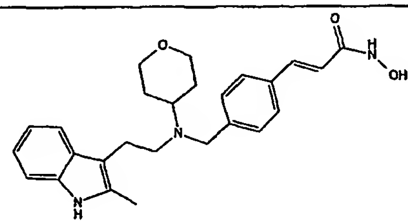
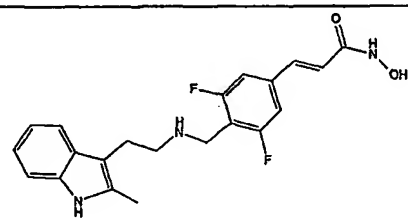
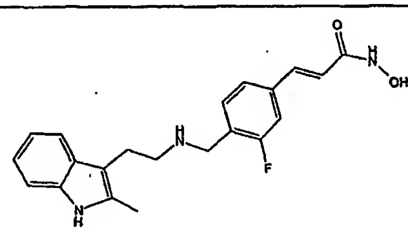
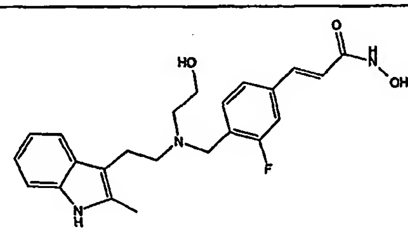
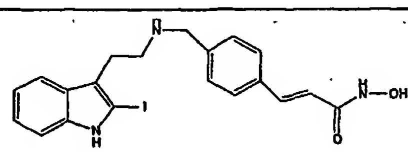
Example	STRUCTURE	m/z (MH⁺)
225		456
226		364
227		481
228		355
229		312
230		424

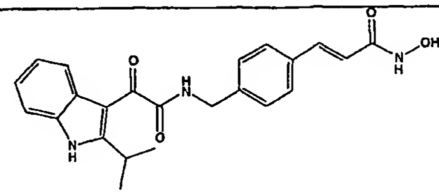
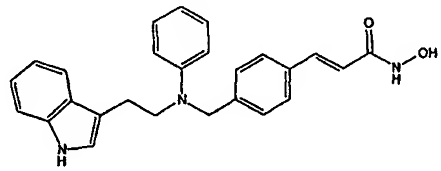
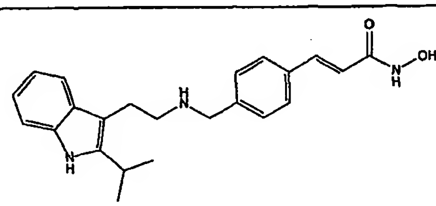
Example	STRUCTURE	m/z (MH+)
231		
232		351
233		392
234		
235		
236		322
237		

Example	STRUCTURE	m/z (MH+)
238		366
239		
240		368
241		
242		406
243		398
244		442

Example	STRUCTURE	m/z (MH⁺)
245		350
246		364
247		402
248		418
249		364
250		

Example	STRUCTURE	m/z (MH⁺)
251		408
252		
253		
254		413
255		405
256		

Example	STRUCTURE	m/z (MH⁺)
257		394
258		390
259		434
260		386
261		368
262		412

Example	STRUCTURE	m/z (MH^+)
263		406
264		
265		378

The compounds of Examples 1-265 show an HDA enzyme IC_{50} in the range from about 0.005 to about 0.5 μM.

Example B1

Cell lines H1299 (human lung carcinoma cell) and HCT116 (colon tumor cell) are obtained from the American Type Culture Collection, Rockville, MD. The cell lines are free of *Mycoplasma* contamination (Rapid Detection System by Gen-Probe, Inc., San Diego, CA) and viral contamination (MAP testing by MA BioServices, Inc., Rockville, MD). The cell lines are propagated and expanded in RPMI 1640 medium containing 10% heat-inactivated FBS (Life Technologies, Grand Island, NY). Cell expansions for implantation are performed in cell factories (NUNC, purchased from Fisher Scientific, Springfield, NJ). Cells are harvested at 50-90% confluency, washed once with HBSS (Hank's Balanced Salt Solution) containing 10% FBS, and suspended in 100% HBSS.

Cell proliferation is measured with a commercial MTS kit (Promega, Madision, Wis.) assay using an adaptation of published procedures, for example, that disclosed in *Feasibility of drug screening with panels of human tumor cell lines using a microculture tetrazolium assay*, Alley MC, et al., Cancer Res. 1988; 48:589-601. Cells are plated in 96-well tissue culture dishes, with top and bottom rows left empty. H1299 and HCT116 cells

are suspended in complete media at a density of 5.3×10^3 and 3.6×10^3 cell/mL, respectively, and 190 µl are added per well. Each cell line is added to one half of the plate. Complete medium (200 µL) is added to the top and bottom rows. Twenty-four hours later, 10 µl of MTS solution is added to one of the plates to determine the activity at the time of compound addition (T_0). The plate is incubated at 37 °C for 4 hours and the OD_{490} is measured on a Molecular Devices Thermomax at 490 nm using the Softmax program. The T_0 plate serves as a reference for initial activity at the beginning of the experiment.

Five serial dilutions (1:4) of each compound are made in a 96-deep well plate with the highest concentrations on the edge of plate. Two cell lines are tested with two compounds per plate. Ten microliters of each of the five dilutions are added in triplicate and complete medium alone is added to columns six and seven. The plates are incubated at 37 °C for 72 hours. The MTS solution is added (as for the T_0 plate) and read four hours later.

In order to analyze the data, the average background value (media alone) is subtracted from each experimental well; the triplicate values are averaged for each compound dilution. The following formulas are used to calculate percent growth.

If $X > T_0$, % Growth = $((X-T_0)/(GC-T_0)) \times 100$

If $X < T_0$, % Growth = $(X-T_0)/T_0) \times 100$

in which T_0 = (average value of cell viability at time 0) – background

GC = average value of untreated cells (in triplicate) – background

X = average value of compound treated cells (in triplicate) – background

The "% Growth" is plotted against compound concentration and used to calculate IC_{50}s employing the linear regression techniques between data points to predict the concentration of compounds at 50% inhibition.

Lactate salts of N-hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide (CMD1), N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide (CMD2), N-hydroxy-3-[4-[[[2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide (CMD3), N-hydroxy-3-[4-[[[2-(5-fluoro-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide (CMD4), N-hydroxy-3-[4-[[[2-(benzofur-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide (CMD5) having a purity of higher than 95% are dissolved in pure dimethylsulfoxide (DMSO) to create a stock solution. The stock solution is diluted with 5% dextrose injection, USP, just prior to dosing. In addition, N-(2-aminophenyl)-4-[N-pyridin-3-yl)methoxycarbonylaminomethyl]benzamide is synthesized in accordance with Example 48 of EP 0 847 992 and used as a control compound (CMDC). Inhibition of cell growth in monolayer for 72 hours of compound treatment is measured in

triplicate experiments and used to derive the IC_{50} by MTS assay. The results are shown in Table B1.

Table B1

	Monolayer Growth IC_{50} (μM)	
Compound	H1299	HCT116
CMD1	0.40	0.03
CMD2	0.15	0.01
CMD3	0.58	0.03
CMD4	0.28	0.03
CMD5	0.18	0.03
CMDC	6.8	0.67

The results show that the hydroxamate compounds of the present invention are highly active in inhibition of tumor cell growth. In addition to the above results, it has been observed that the compounds selectively inhibited tumor cells while showing minimal inhibition activities in non-tumorous cells.

The cells treated with the hydroxamate compounds are also tested for the induction of p21 promoter, which is a key mediator of G1 arrest and differentiation. The hydroxamate compounds activate the p21 promoter to a readily detectable level at a concentration within two-fold of their respective IC_{50} for monolayer cell growth inhibition in H1299. Without being bound by any particular theory, the correlation appears to demonstrate that HDA inhibition leads to transcriptional activation of genes that inhibit tumor cell proliferation.

Example B2

HDA is partially purified from H1299, human non-small cell lung carcinoma cells (obtained from American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852, USA). Cells are grown to 70-80% confluence in RPMI media in the presence of 10% FCS, harvested and lysed by sonication. The lysate is centrifuged at 23, 420g for 10-15 min, the supernatant is applied to a Hiload 26/10 High performance Q-sepharose column (Amersham Pharmacia Biotech), and equilibrated with a buffer containing 20 mM Tris

pH8.0, 1 mM EDTA, 10 mM NH_4Cl_2, 1 mM β-Mercaptoethanol, 5% glycerol, 2 μg/mL aprotinin, 1 μg/mL leupeptin, and 400 mM PMSF. Proteins are eluted in 4mL aliquotes with a linear gradient from 0-500 mM NaCl in the above buffer at a flow rate of 2.5 mL/min. Each preparation of partially purified HDA enzyme is titrated to determine the optimal amount needed to obtain a signal to noise ratio of at least 5 to 1. Generally, 20-30 μl of partially purified HDA (5-10 mg protein/mL) is mixed with 2 μL of compound solution in DMSO in a deep well titer plate (Beckman). The compounds are serially diluted in DMSO to generate stocks at 20-fold of the assay concentrations. Final concentrations of compounds in the assay are 10 μM, 2 μM, 400 nM, 80 nM, and 16 nM with the final percentage of DMSO in each enzyme reaction equaling 0.1%. Each concentration of compound is assayed in duplicate. The substrate used in the reaction is a peptide of amino acid sequence, SGRGKGGKGLGKGGAKRHRKVLRD, corresponding to the twenty-four N-terminal amino acids of human histone H4, biotinylated at the N-terminus and penta-acetylated, at each lysine residue with ^{3}H-acetate. To initiate the reaction, the substrate is diluted in 10 μL of Buffer A (100 mM Tris pH 8.0, 2 mM EDTA), added to the enzyme mixture and collected at the bottom of the deep well plate by centrifugation for 5 minutes at 1500 rpm. Following centrifugation, the mixture is incubated at 37 °C for 1.5 hr. The reaction is stopped by the addition of 20 μL of the Stop Buffer (0.5N HCl, 0.08M Acetic Acid). At this point, the assay proceeds to the robotic extraction phase or is frozen for several days at –80 °C.

The extraction of enzymatically cleaved ^{3}H-acetate groups from the reaction mixture is achieved with the solvent TBME (t-butyl methyl ether) using the Tomtec Quadra 96 workstation. A program is written to add 200 μL of TBME to a 96 "deep well" plate. The workstation is programmed to aspirate 50 μL of air followed by 200 μL of TBME and finally another 25 μL of air, which is dispensed into the each well of the plate. The contents of the deep well were mixed thoroughly by pipetting 160 μL up and down 10 times. Before addition of TBME to the reaction mixture, it is necessary to "pre-wet" the pipette tips with TBME to prevent the solvent from dripping during the transfer to the deep well plate. The organic and aqueous phases in the deep well are separated by centrifugation at 1500 rpm for 5 min. Opti-Phase Supermix liquid scintillation cocktail (200 μL) (Wallac) is added to each well of the 96-well Trilux plate (Wallac). The deep well and Trilux plates are placed back on the workstation programmed to aspirate 25 μL of air into the pipette tips followed by 100 μL of the upper TBME phase and transfer it into the Trilux plate. The solutions are mixed by pipetting and expelling 50 μL, five times, within the same well. The Trilux plate is

covered with clear film and read on a 1450 MicroBeta Trilux liquid scintillation and luminescence counter (Wallac) with a color/chemical quench and dpm correction.

In order to determine the IC_{50} values, the data are analyzed on a spreadsheet. The analysis requires a correction for the background luminescence that is accomplished by subtracting the dpm values of wells without ^3H substrate from the experimental wells. The corrected dpm values along with the concentrations of the compounds are used to calculate IC_{50} using the user-defined spline function. This function utilizes linear regression techniques between data points to calculate the concentration of compounds that produced 50% inhibition. The results are shown in Table B2.

Table B2

Compound	HDA Enzyme Activity IC_{50} (μM)
CMD1	0.032
CMD2	0.063
CMD3	0.014
CMD4	0.014
CMD5	0.016
CMDC	> 10

Example B3

The A549 non-small cell lung human tumor cell line is purchased from the American Type Culture Collection, Rockville, MD. The cell line is free of *Mycoplasma* contamination (Rapid Detection System by Gen-Probe, Inc., San Diego, CA) and viral contamination (MAP testing by MA BioServices, Inc., Rockville, MD). The cell line is propagated and expanded in RPMI 1640 medium containing 10% heat-inactivated FBS (Life Technologies, Grand Island, NY). Cell expansions for implantation are performed in cell factories (NUNC, purchased from Fisher Scientific, Springfield, NJ). Cells are harvested at 50-90% confluency, washed once with HBSS containing 10% FBS, and suspended in 100% HBSS.

Outbred athymic (*nu/nu*) female mice ("Hsd:Athymic Nude-nu" from Harlan Sprague Dawley, Indianapolis, IN) are anesthetized with Metofane (Mallinckrodt Veterinary, Inc.,

Mundelein, IL), and 100 μL of the cell suspension containing 1×10^7 cells is injected subcutaneously into the right axillary (lateral) region of each animal. Tumors are allowed to grow for about 20 days until a volume of ~100 mm^3 is achieved. At this point, mice bearing tumors with acceptable morphology and size are sorted into groups of eight for the study. The sorting process produces groups balanced with respect to mean and range of tumor size. Antitumor activity is expressed as % T/C, comparing differences in tumor volumes for treatment group (T) to vehicle control group (C). Regressions are calculated using the formula: $(1-T/T_0) \times 100\%$, where T is the tumor volume for the treatment group at the end of the experiment, and T_0 is the tumor volume at the beginning of the experiment.

CMD1 is administered intravenously, once daily 5x/week for three weeks, at doses of 10, 25, 50, or 100 mg/kg. The final DMSO concentration is 10%. Each test group has eight mice. Tumors are measured, and individual animal body weights recorded. Table B3 shows the results on the 41st day.

Table B3

COMPOUND	DOSE (mg/kg)	Δ MEAN TUMOR VOLUME*1 (mm^3 ± SEM*3)	% T/C	Δ % BODY WEIGHT*2 (% ± SEM*3)
10% DMSO/D5W*4	-	376 ± 55	-	+11.9 ± 0.2
CMD1	10	121 ± 27	32	+ 1.3 ± 0.3
CMD1	25	77 ± 32	20	- 0.9 ± 0.3
CMD1	50	57 ± 10	15	- 0.4 ± 0.3
CMD1	100	28 ± 25	7	+ 0.4 ± 0.3

Note: *1. Difference in mean tumor volume for a group of animals at the end of the experiment minus mean tumor volume at the beginning.

*2. Difference in body weight for a group of animals at the end of the experiment minus mean tumor volume at the beginning.

*3. Standard error of the mean.

*4. 5% dextrose injection, USP.

Example B4

Example B3 repeated except CMD2 is used. Table B4 shows the results.

Table B4

COMPOUND	DOSE (mg/kg)	Δ MEAN TUMOR VOLUME (mm^3 ± SEM)	% T/C	Δ % BODY WEIGHT (% ± SEM)
10% DMSO/D5W	-	135 ± 43	-	+ 6.7 ± 1.1
CMD2	25	37 ± 16	27	- 4.2 ± 2.5
CMD2	50	29 ± 15	21	- 2.9 ± 1.5

Example B5

Example B3 is repeated except the HCT116 colon tumor cell line is used in place of the A549 cell line. The HCT116 cell line is also obtained from American Type Culture Collection, Rockville, MD, and the cell line is free of *Mycoplasma* contamination and viral contamination. The results are recorded on the 34th day and are shown in Table B5.

Table B5

COMPOUND	DOSE (mg/kg)	Δ MEAN TUMOR VOLUME (mm^3 ± SEM)	% T/C	Δ % BODY WEIGHT (% ± SEM)
10% DMSO/D5W	-	759 ± 108	-	- 0.4 ± 0.4
CMD1	50*10	186 ± 40	25	- 7.4 ± 0.8
CMD1	100	140 ± 38	18	- 3.2 ± 0.4

Note: *10. Seven mice are tested in this group.

Example B6

Example B4 is repeated except the HCT116 colon tumor cell line is used in place of the A549 cell line. The HCT116 is also obtained from American Type Culture Collection, Rockville, MD, and the cell line is free of *Mycoplasma* contamination and viral contamination. The results are recorded on the 34th day and are shown in Table B6.

Table B6

COMPOUND	DOSE (mg/kg)	Δ MEAN TUMOR VOLUME (mm^3 ± SEM)	% T/C	Δ % BODY WEIGHT (% ± SEM)
10% DMSO/D5W	-	759 ± 108	-	- 0.4 ± 0.4
CMD2	10	422 ± 75	56	- 10.2 ± 0.5
CMD2	25	305 ± 47	40	- 7.0 ± 0.2
CMD2	50	97 ± 30	13	- 7.3 ± 0.3
CMD2	100	132 ± 30	17	- 9.4 ± 0.4

Example B7

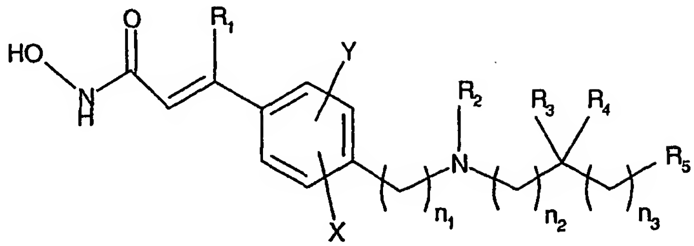
Annexin V binding was used as a marker for the early stages of apoptosis. A549, HCT116 and Normal Dermal Human Fibroblasts (NDHF) cells are treated separately with four compounds (CMD1, CMD2, CMD3 and CMD4) for 24 or 48 hours, stained with annexin V and compared to cells treated similarly with vehicle (DMSO). Cells are examined by fluorescence microscopy. Those undergoing apoptosis exhibit green fluorescent membrane staining. Viability is assessed by the counterstain, propidium iodide. Cells detected by red fluorescence are not viable. A small percentage of A549 and the majority of HCT116 cells exhibit cell surface staining with annexin V after 24 hour exposure to each of the four compounds. After 48 hour treatment, the majority of the A549 and HCT116 stain with annexin V and/or propidium iodide indicating that the compounds induce apoptotic cell death. In contrast, NDHF cells do not show noticeable annexin V staining after 24 hour exposure and limited annexin V staining with CMD3 after 48 hour. These data show that

NDHF cells predominantly underwent non-lethal growth arrest upon compound treatment, consistent with the cell cycle profile.

The staining results demonstrate that the hydroxamate compounds of the present invention cause tumor cells to die by apoptosis, while causing normal fibroblast to predominantly undergo cell cycle arrest, clearly demonstrating the selective efficacy of the present compounds.

What is claimed is:

1. A compound of the formula I



(I)

wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl;

R_2 is selected from H, C_1-C_{10} alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, $C_4 - C_9$ heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, $-(CH_2)_nOC(O)R_6$, amino acyl, HON-C(O)-CH=C(R_1)-aryl-alkyl- and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound represent C=O, C=S, or C=NR_8, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound can form a $C_4 - C_9$ heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, and mixed aryl and non-aryl polyheterocycle;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0 – 6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, NO_2, C(O)R_1, OR_9, SR_9, CN, and $NR_{10}R_{11}$;

R_6 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR_{12}, and $NR_{13}R_{14}$;

R_7 is selected from OR_{15}, SR_{15}, $S(O)R_{16}$, SO_2R_{17}, $NR_{13}R_{14}$, and $NR_{12}SO_2R_6$;

R_8 is selected from H, OR_{15}, $NR_{13}R_{14}$, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R_9 is selected from $C_1 - C_4$ alkyl and C(O)-alkyl;

R_{10} and R_{11} are the same or different and independently selected from H, C_1-C_4 alkyl, and -C(O)-alkyl;

R_{12} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, $C_4 - C_9$ heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl, and heteroarylalkyl;

R_{13} and R_{14} are the same or different and independently selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, amino acyl, or R_{13} and R_{14} together with the nitrogen to which they are bound are $C_4 - C_9$ heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R_{15} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{16} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{17} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, aromatic polycycle, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and $NR_{13}R_{14}$;

m is an integer selected from 0 to 6; and

Z is selected from O, NR_{13}, S and S(O);

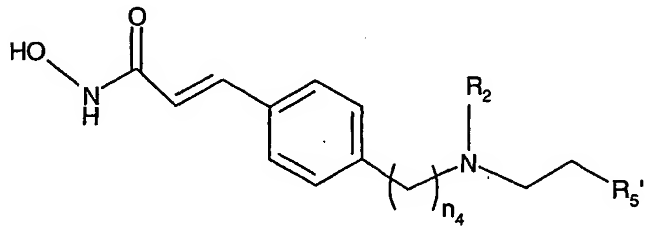
or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein each of R_1, X, Y, R_3, and R_4 is H.

3. A compound of claim 2 wherein one of n_2 and n_3 is zero and the other is 1.

4. A compound of claim 3 wherein R_2 is H or $-CH_2$-CH_2-OH.

5. A compound of claim 1 of the formula Ia



(Ia)

wherein

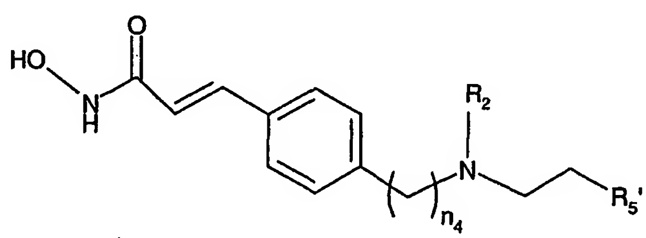
n_4 is 0-3,

R_2 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, -$(CH_2)_nC(O)R_6$, amino acyl and -$(CH_2)_nR_7$;

R_5' is heteroaryl, heteroarylalkyl, an aromatic polycycle, a non-aromatic polycycle, a mixed aryl and non-aryl polycycle, polyheteroaryl, or a mixed aryl and non-aryl polyheterocycle,

or a pharmaceutically acceptable salt thereof.

6. A compound of claim 1 of the formula Ia



(Ia)

wherein

n_4 is 0-3,

R_2 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, -$(CH_2)_nC(O)R_6$, amino acyl and -$(CH_2)_nR_7$;

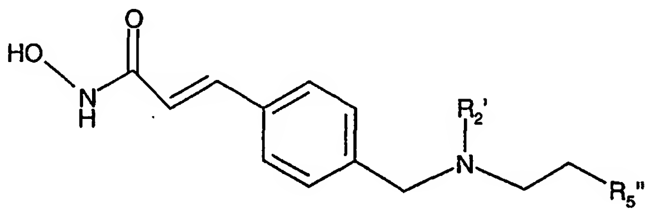
R_5' is aryl, arylalkyl, an aromatic polycycle, a non-aromatic polycycle or a mixed aryl and non-aryl polycycle,

or a pharmaceutically acceptable salt thereof.

7. A compound of claim 6 wherein R_5' is aryl or arylalkyl.

8. A compound of claim 7 wherein R_5' is p-fluorophenyl, p-chlorophenyl, p-O-C_1-C_4-alkylphenyl, p-C_1-C_4-alkylphenyl, benzyl, ortho, meta or para-fluorobenzyl, ortho, meta or para-chlorobenzyl, or ortho, meta or para - mono, di or tri-O-C_1-C_4-alkylbenzyl.

9. A compound of claim 1 of the formula Ib



(Ib)

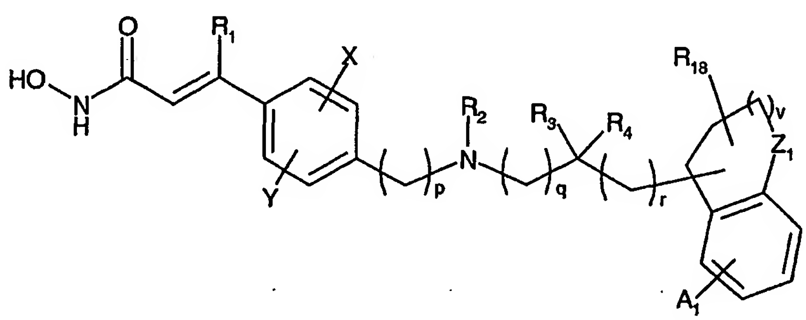
wherein

R_2' is selected from H, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, cycloalkylalkyl, -$(CH_2)_{2\text{-}4}OR_{21}$ where R_{21} is H, methyl, ethyl, propyl, or isopropyl, and

R_5" is unsubstituted or substituted 1*H*-indol-3-yl, benzofuran-3-yl or quinolin-3-yl, or a pharmaceutically acceptable salt thereof.

10. A compound of claim 9 wherein R_5" is substituted 1*H*-indol-3-yl or substituted benzofuran-3-yl.

11. A compound of claim 1 of the formula Ic



(Ic)

wherein

the ring containing Z_1 is aromatic or non-aromatic which non-aromatic rings are saturated or unsaturated,

Z_1 is O, S or N-R_{20};

R_{18} is H, halo, C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl, or heteroaryl;

R_{20} is H, C_1-C_6alkyl, C_1-C_6alkyl-C_3–C_9cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, acyl or sulfonyl;

A_1 is 1, 2 or 3 substituents which are independently H, C_1-C-$_6$alkyl, -OR_{19}, halo, alkylamino, aminoalkyl, halo, or heteroarylalkyl;

R_2 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, -$(CH_2)_nC(O)R_6$, amino acyl and -$(CH_2)_nR_7$;

R_{19} is selected from H, C_1-C_6alkyl, C_4–C_9cycloalkyl, C_4–C_9heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

v is 0, 1 or 2,

p is 0-3, and

q is 1-5 and r is 0 or

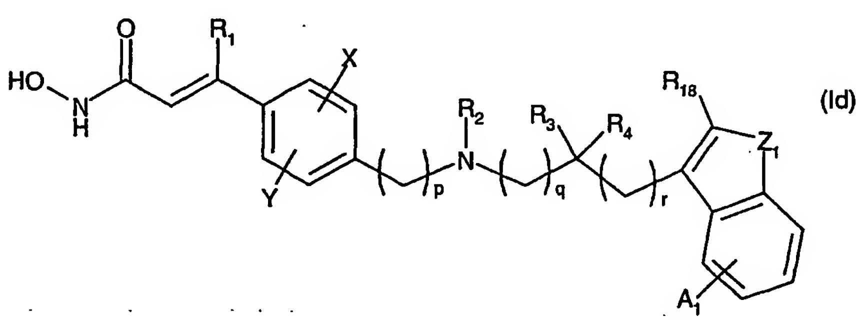
q is 0 and r is 1-5,

or a pharmaceutically acceptable salt thereof.

12. A compound of claim 11 wherein Z_1 is N-R_{20}.

13. A compound of claim 11 wherein R_2 is H or –CH_2-CH_2-OH and the sum of q and r is 1.

14. A compound of claim 1 of the formula Id



(Id)

wherein

Z_1 is O, S or N-R_{20},

R_{18} is H, halo, C_1-C_6alkyl, C_3-C_7cycloalkyl, unsubstituted phenyl, substituted phenyl, or heteroaryl,

R_{20} is H, C_1-C_6alkyl, C_1-C_6alkyl-C_3–C_9cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, acyl or sulfonyl;

A_1 is 1, 2 or 3 substituents which are independently H, C_1-C-$_6$alkyl, -OR_{19}, or halo,

R_{19} is selected from H, C_1-C_6alkyl, C_4–C_9cycloalkyl, C_4–C_9heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and -$(CH_2CH{=}CH(CH_3)(CH_2))_{1\text{-}3}H$;

p is 0-3, and

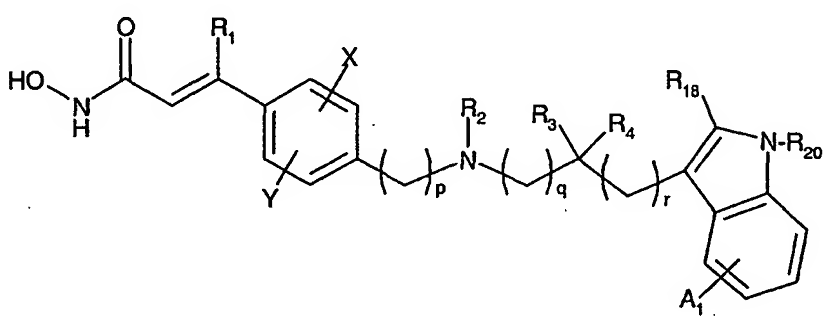
q is 1-5 and r is 0 or

q is 0 and r is 1-5,

or a pharmaceutically acceptable salt thereof.

15. A compound of claim 14 wherein R_2 is H or –CH_2-CH_2-OH and the sum of q and r is 1.

16. A compound of claim 11 of the formula Ie



(Ie)

or a pharmaceutically acceptable salt thereof.

17. A compound of claim 16 wherein R_{18} is H, fluoro, chloro, bromo, C_1-C_4alkyl, C_3-C_7cycloalkyl, phenyl or heteroaryl.

18. A compound of claim 16 wherein R_2 is H, or -$(CH_2)_pCH_2OH$ and wherein p is 1-3.

19. A compound of claim 18 wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3.

20. A compound of claim 16 wherein R_{18} is H, methyl, ethyl, t-butyl, trifluoromethyl, cyclohexyl, phenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 2-furanyl, 2-thiophenyl, or 2-, 3- or 4-pyridyl.

21. A compound of claim 20 wherein R_2 is H, or $-(CH_2)_pCH_2OH$.

22. A compound of claim 21 wherein p is 1-3.

23. A compound of claim 22 wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3.

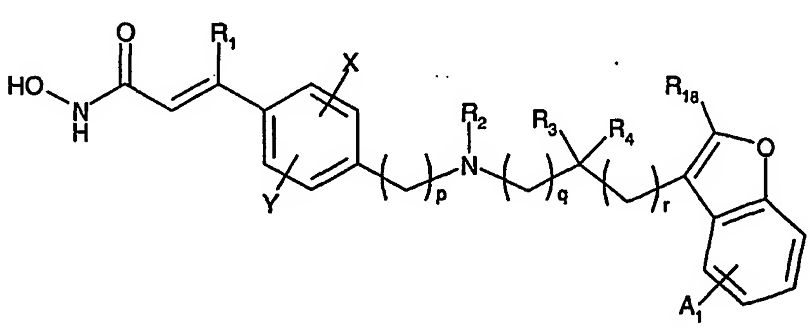
24. A compound of claim 23 wherein R_2 is H or $-CH_2-CH_2-OH$ and the sum of q and r is 1.

25. A compound of claim 16 wherein R_{20} is H or C_1-C_6alkyl.

26. A compound of claim 16 selected from the group consisting of N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide and N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.

27. A compound of claim 26 which is N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof.

28. A compound of claim 1 of the formula If



(If)

or a pharmaceutically acceptable salt thereof.

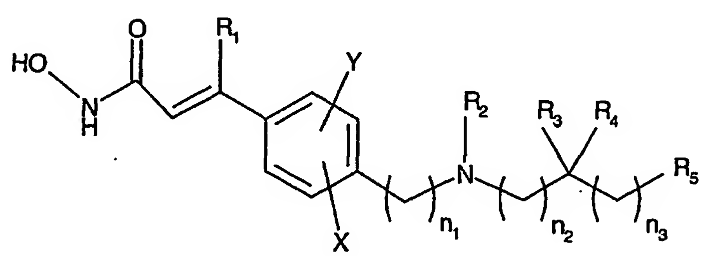
29. A compound of claim 28 wherein R_2 is H or $-(CH_2)_pCH_2OH$ and p is 1-3.

30. A compound of claim 29 wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3.

31. A compound of claim 30 wherein R_2 is H or $-CH_2-CH_2-OH$ and the sum of q and r is 1.

32. A compound of claim 28 which is N-hydroxy-3-[4-[[[2-(benzofur-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.

33. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula I



(I)

wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl;

R_2 is selected from H, C_1-C_{10} alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, $-(CH_2)_nOC(O)R_6$, amino acyl, HON-C(O)-CH=C(R_1)-aryl-alkyl- and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound represent C=O, C=S, or C=NR_8, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound can form a C_4-C_9 heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, and mixed aryl and non-aryl polyheterocycle;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0 – 6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, NO_2, $C(O)R_1$, OR_9, SR_9, CN, and $NR_{10}R_{11}$;

R_6 is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR_{12}, and $NR_{13}R_{14}$;

R_7 is selected from OR_{15}, SR_{15}, $S(O)R_{16}$, SO_2R_{17}, $NR_{13}R_{14}$, and $NR_{12}SO_2R_6$;

R_8 is selected from H, OR_{15}, $NR_{13}R_{14}$, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R_9 is selected from C_1-C_4 alkyl and C(O)-alkyl;

R_{10} and R_{11} are the same or different and independently selected from H, C_1-C_4 alkyl, and -C(O)-alkyl;

R_{12} is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl, and heteroarylalkyl;

R_{13} and R_{14} are the same or different and independently selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, amino acyl, or R_{13} and R_{14} together with the nitrogen to which they are bound are C_4-C_9 heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R_{15} is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{16} is selected from C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{17} is selected from C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, aromatic polycycle, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and $NR_{13}R_{14}$;

m is an integer selected from 0 to 6; and

Z is selected from O, NR_{13}, S and S(O);

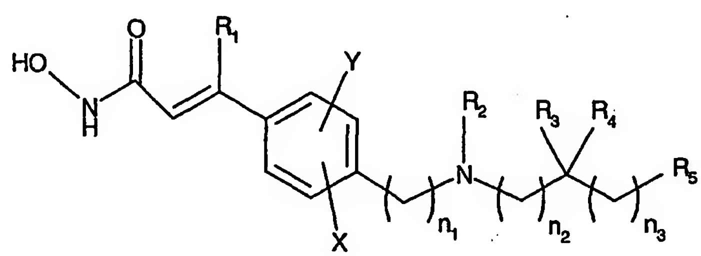
or a pharmaceutically acceptable salt thereof.

34. A pharmaceutical composition of claim 33 wherein the compound of formula I is selected from the group consisting of N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide and N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition of claim 34 wherein the compound of formula I is N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition of claim 33 wherein the compound of formula I is N-hydroxy-3-[4-[[[2-(benzofur-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.

37. A method for treating a proliferative disorder in a mammal which comprises administering to said mammal a compound of the formula I



(I)

wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl;

R_2 is selected from H, C_1-C_{10} alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, $-(CH_2)_nOC(O)R_6$, amino acyl, HON-C(O)-CH=C(R_1)-aryl-alkyl- and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound represent

C=O, C=S, or C=NR_8, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound can form a $C_4 - C_9$ heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, and mixed aryl and non-aryl polyheterocycle;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0 – 6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, NO_2, $C(O)R_1$, OR_9, SR_9, CN, and $NR_{10}R_{11}$;

R_6 is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR_{12}, and $NR_{13}R_{14}$;

R_7 is selected from OR_{15}, SR_{15}, $S(O)R_{16}$, SO_2R_{17}, $NR_{13}R_{14}$, and $NR_{12}SO_2R_6$;

R_8 is selected from H, OR_{15}, $NR_{13}R_{14}$, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R_9 is selected from $C_1 - C_4$ alkyl and C(O)-alkyl;

R_{10} and R_{11} are the same or different and independently selected from H, C_1-C_4 alkyl, and -C(O)-alkyl;

R_{12} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, $C_4 - C_9$ heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl, and heteroarylalkyl;

R_{13} and R_{14} are the same or different and independently selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, amino acyl, or R_{13} and R_{14} together with the nitrogen to which they are bound are $C_4 - C_9$ heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R_{15} is selected from H, C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{16} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{17} is selected from C_1-C_6 alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, aryl, aromatic polycycle, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and $NR_{13}R_{14}$;

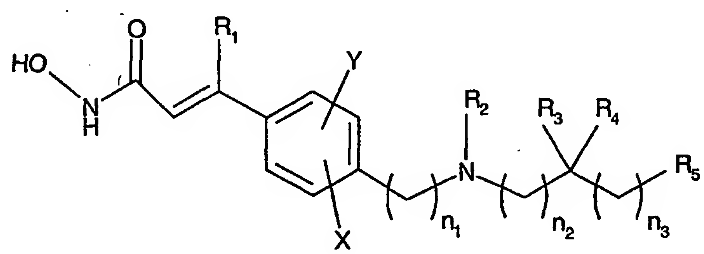
m is an integer selected from 0 to 6; and

Z is selected from O, NR_{13}, S and S(O);

or a pharmaceutically acceptable salt thereof.

38. A method of claim 37 wherein the compound of formula I is selected from the group consisting of N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide and N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.

39. A method for regulating p21 promoter which comprises introducing a compound of the formula I



(I)

wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl;

R_2 is selected from H, C_1-C_{10} alkyl, $C_4 - C_9$ cycloalkyl, $C_4 - C_9$ heterocycloalkyl, $C_4 - C_9$ heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, $-(CH_2)_nOC(O)R_6$, amino acyl, HON-C(O)-CH=C(R_1)-aryl-alkyl- and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound represent C=O, C=S, or $C=NR_8$, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound can form a $C_4 - C_9$ heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, and mixed aryl and non-aryl polyheterocycle;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0 – 6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, NO_2, $C(O)R_1$, OR_9, SR_9, CN, and $NR_{10}R_{11}$;

R_6 is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR_{12}, and $NR_{13}R_{14}$;

R_7 is selected from OR_{15}, SR_{15}, $S(O)R_{16}$, SO_2R_{17}, $NR_{13}R_{14}$, and $NR_{12}SO_2R_6$;

R_8 is selected from H, OR_{15}, $NR_{13}R_{14}$, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R_9 is selected from C_1-C_4 alkyl and C(O)-alkyl;

R_{10} and R_{11} are the same or different and independently selected from H, C_1-C_4 alkyl, and -C(O)-alkyl;

R_{12} is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl, and heteroarylalkyl;

R_{13} and R_{14} are the same or different and independently selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, amino acyl, or R_{13} and R_{14} together with the nitrogen to which they are bound are C_4-C_9 heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R_{15} is selected from H, C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{16} is selected from C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{17} is selected from C_1-C_6 alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, aromatic polycycle, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and $NR_{13}R_{14}$;

m is an integer selected from 0 to 6; and

Z is selected from O, NR_{13}, S and S(O);

or a pharmaceutically acceptable salt thereof,

into the environment of a mammalian cell.

40. A method of claim 39 wherein the compound of formula I is selected from the group consisting of N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide and N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.